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OF

# INTERNAL MEDICINE

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VOLUME 50  
1932

PUBLISHERS

AMERICAN MEDICAL ASSOCIATION  
CHICAGO





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## DIFFUSE HEMORRHAGE FROM THE STOMACH

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PHILADELPHIA

Diffuse bleeding from the gastric mucosa is regarded as a relatively unimportant phenomenon and is rarely, if ever, considered in the bedside diagnosis of patients afflicted with hematemesis. When the patient vomits blood, the differential diagnosis, as a rule, takes into consideration the following possibilities:

### *The Most Common Causes of Gastric Hemorrhage*

#### A *Neoplasms*

Carcinoma

Polypi

#### B *Ulcers*

Acute

Subacute and progressive

Chronic

#### C *Infections—Acute or Chronic* (May cause either a local ulcer or a diffuse gastritis)

##### 1 Intra-abdominal (colitis, enteritis, gastritis)

appendicitis

disease of the biliary tract

tuberculosis

typhoid

##### 2 Extra-abdominal

scarlet fever

yellow fever

measles

cellulitis

pneumonia

diphtheria

endocarditis

##### 3 Disease of the upper respiratory tract

##### 4 Pelvic disease

##### 5 Alcoholism

#### D *Systemic Diseases*

##### 1 Cardiovascular

heart failure

endocarditis

thromboses or emboli

hypertension

aneurysms

ruptured varices

esophagus

rectum and anus (especially)

- 2 Blood dyscrasias
  - leukemia
  - the purpuras
- 3 Renal disease
- 4 Cirrhosis
- 5 Syphilis
- 6 Allergy (urticaria)

#### E *Corrosion*

From ingestion of poisons, as chloride, iodine, lye, etc

The clinical syndrome which characterizes each of the aforementioned states is so definite that little difficulty should be experienced in narrowing the diagnosis to the logical underlying lesion. However, the certitude of successful diagnosis is more apparent than real. The survey of a large number of cases in which the outstanding sign was hematemesis suggests that hemorrhage from the stomach may arise from one or more of several different mucosal lesions and may be due to other inciting factors.

#### 1 DIFFUSE GASTRIC HEMORRHAGE DUE TO PHYSICAL OR EMOTIONAL STRAIN

Warren<sup>1</sup> in 1881 noted that the female sex seems to suffer from hematemesis more frequently than the male, that it may occur at any age, and that sometimes it seems to take place spontaneously but really is due to some exciting cause that in itself might be insufficient to produce hemorrhage in a sound gastric membrane but is able to effect a rupture when any tendency to hemorrhage already exists. Under this heading he mentioned mental excitement, strain, concussions of the body and overdistentions of the stomach. He believed that injurious pressure could come on the internal organs, causing various forms of trouble especially in women, and cited the following case:

A woman, 25 years of age, taught in the public schools and lived at home with her parents. She had no hereditary predisposition to any disease and always considered herself healthy in every respect. After taking singing lessons by the "Abdominal Method or Elocution Breathing" for a while, she was troubled by what she thought was dyspepsia, and she took the usual remedies, without benefit. Five months after the onset of this gastric distress and the day after taking a lesson, she vomited over a pint of dark, bloody fluid. Within the next ten days there were seven recurrences of hematemesis, the blood being at times bright red and at times dark. This patient was given medical treatment in her home, and the hemorrhage finally ceased.

Alvarez<sup>2</sup> cited a case in which diffuse gastric hemorrhage occurred from an apparently healthy mucous membrane due to mental excitement.

<sup>1</sup> Warren, E. L. *Gastrorrhagia and Hematemesis, with a Case*, Boston M & S J **104** 417, 1881.

<sup>2</sup> Alvarez, W. C. *Nervous Indigestion*, New York, Paul B. Hoeber, Inc., 1931, p. 58.

A man, an inventor, after years of poverty induced one of the richest industries of the country to accept his machine. The patient saw wealth and comfort within his grasp, but a few months later, with a change in the raw product that was being refined, the machine clogged and the company ordered that it be taken out. The patient immediately had a severe gastric hemorrhage. The defect in the machine was overcome, again it failed, and again it was remodeled. This happened at least six times in three years, and on each occasion the patient had a severe hemorrhage.

In both the foregoing cases, the hemorrhage ceased spontaneously, the interior of the stomach was not examined, and the condition present

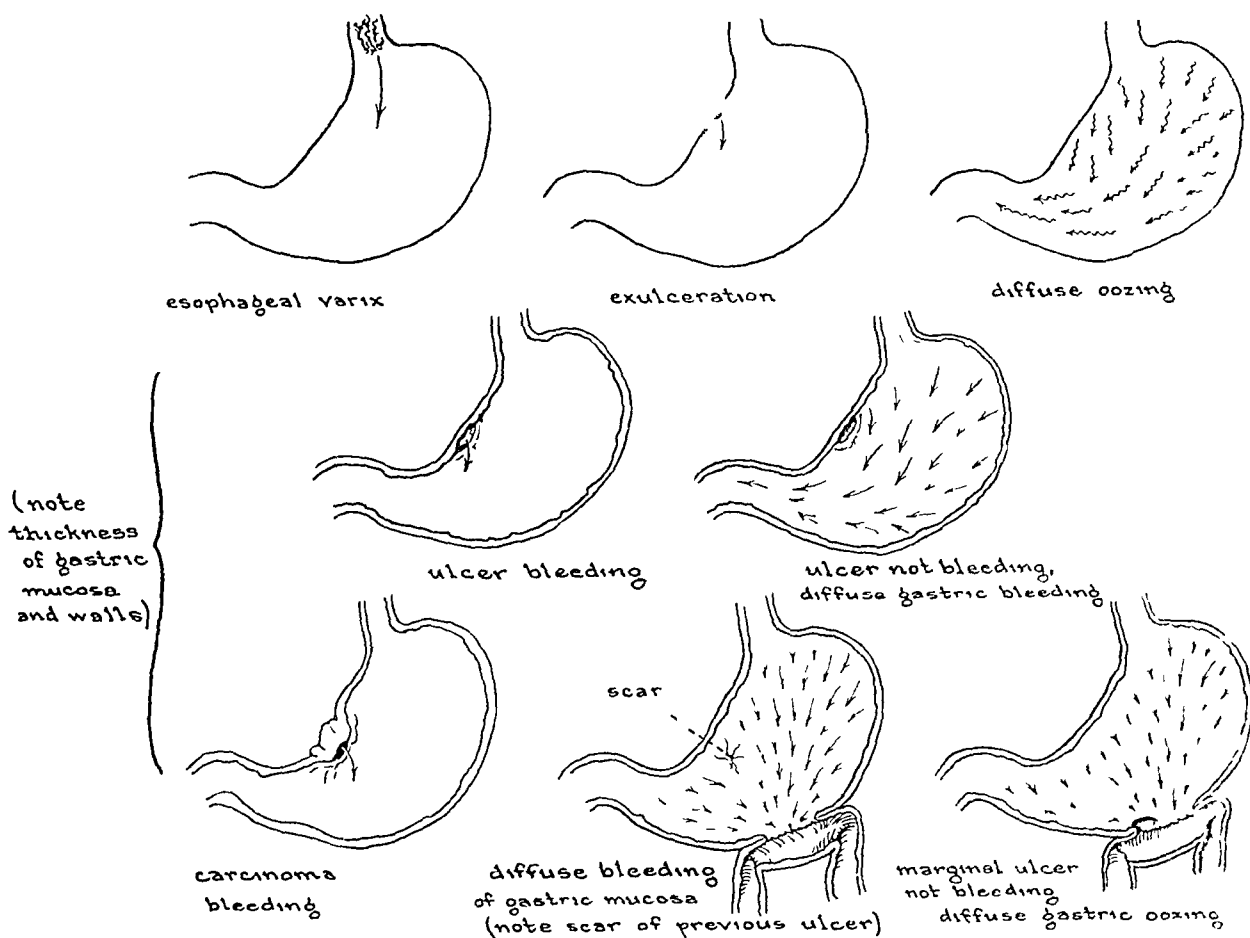


Fig 1—Types of gastric hemorrhage. Gastric hemorrhage may arise from a local lesion, such as a ruptured varix, an ulcer or a neoplasm, diffuse oozing or frank hemorrhage can take place. A chronic ulcer, a marginal ulcer or an ulcer scar has been noted in the mucosa, the seat of diffuse bleeding with no hemorrhage from the ulcer itself.

in the mucosa is not known. In the following case reported by Mayo Robson,<sup>3</sup> which may possibly be of the same kind, the inner surface of the stomach was actually examined and the type of bleeding noted.

3 Robson, A. W. M., and Moynihan, B. G. A. *Diseases of the Stomach and Their Surgical Treatment*, ed 2, New York, William Wood & Company, 1904, p 278.



A married woman, aged 28, while in her home suddenly felt faint and vomited a pint of dark, clotted blood. She seemed to improve under medical treatment, but six days later vomited another large quantity of blood and had melena. Four days after the second attack (the tenth day of the illness) the hematemesis recurred. Since it was evident that the hemorrhage was persisting, the stomach was opened and many bleeding points were found in the mucosa. Three were ligatured *en masse*, and a posterior gastro-enterostomy was performed. The patient was able to be out of bed in the third week and to leave the house within the month. She rapidly regained her strength, had no further hemorrhage and remained in good health.

This patient had been operated on a few months previously for varicose veins, and six weeks previously had had an attack of influenza. However, she felt quite well, and the day before the first hematemesis had been out hunting. It seems probable that in this case it was the strain of hunting that caused the rupture of the capillary walls.

## 2 PROFUSE HEMORRHAGE FROM SUPERFICIAL DEFECTS IN THE MUCOSA

Dieulafoy<sup>4</sup> in 1897 wrote the classic description of the lesion since known as "Dieulafoy's ulcer," a lesion so shallow that at operation as well as post mortem it might pass unperceived without careful examination and a preconceived idea that it was to be found. Only the mucosa was involved (in some cases, including the muscularis mucosae), the edges were neither raised nor thick, and the surrounding tissue was healthy. Often, near the lesion or at its surface, small spots of ecchymotic appearance were noted which were described as miliary abscesses situated in the depths of the mucosa and forcing their way into the cavity of the stomach. At times, the arteriole that was the source of the hemorrhage could be distinguished.

Dieulafoy's first experience with the condition was as follows:

A man, 27 years of age, had had a severe hematemesis, accompanied by pain in the stomach, brought on by lifting a heavy load of papers. After ruling out all the other common causes of severe gastric hemorrhage, it was decided that the hematemesis in this case was due to a gastric ulcer that had evolved without symptoms. The hematemesis reappeared during the night, and it was estimated that the patient had lost about 4 liters of blood in less than twenty-four hours. At 1 o'clock the next afternoon, he died in the midst of another violent hemorrhage. At autopsy, it was only after washing the mucosa with care that a very superficial "exulceration" about the size of a silver dollar was discovered 2 cm from the cardia. The surface of the lesion was a whitish gray with two or three small ecchymotic spots and two crateriform erosions, one of which revealed a small gaping arteriole in which the point of a pin might be introduced and which could be plainly seen only through the microscope. The remainder of the gastric mucosa was in perfect integrity, as was that of the duodenum and esophagus. The

<sup>4</sup> Dieulafoy, G. Exulceratio simplex, Clin méd de Hôtel-Dieu de Paris, 1897-1898, vol 2, lectures 1, 2 and 3.

arteriole was a branch of the gastric coronary artery and had been perfectly healthy when it was attacked by the ulcerous process. The adjacent veins were dilated and thrombosed and explained the ecchymotic spots.

Dieulafoy's second case was as follows:

A man, 22 years of age, was taken with malaise and nausea as he was "returning peacefully home after dining well" and soon afterward vomited "floods of blood." The next day, in order to regain his strength he ate a great deal of food,

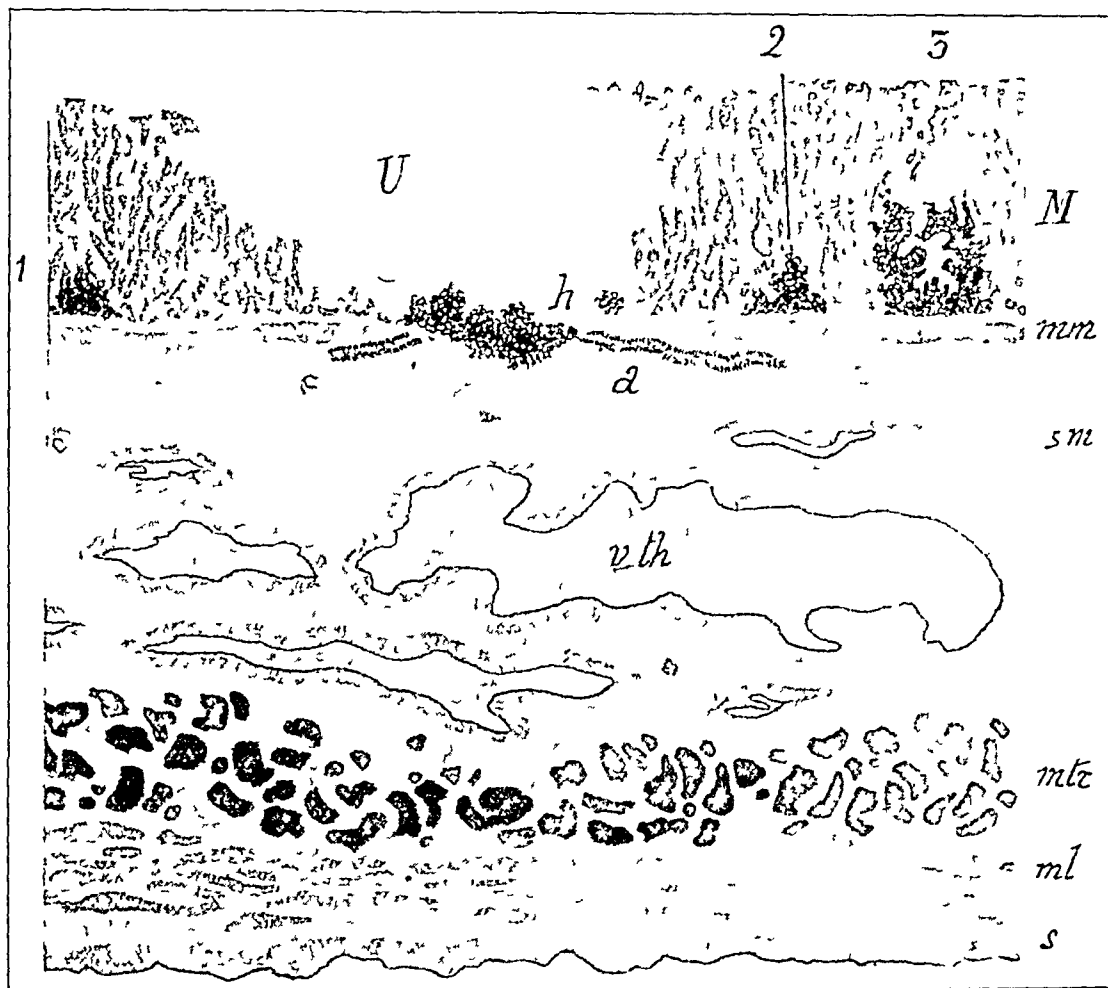


Fig 2—Illustration from Dieulafoy's original paper (*Clinique medicale de l'Hôtel-Dieu de Paris*, Paris, Masson & Cie, 1898, vol 2), showing the details of the ulcerative process. Note the hemorrhage (*h*) and the thrombosed veins (*v th*). *U* indicates ulceration at the expense of the mucosa (*M*) and of the muscularis mucosa (*mm*), *a*, a submucous arteriole destroyed at point *h*, where are to be found many new corpuscles in heaps, at this point have occurred the fatal hemorrhages, *sm*, the submucous layer, *mtz* and *ml*, muscular layers, *s*, serosa and 1, 2 and 3, military abscesses lying in the depth of the mucosa.

especially meat. At 2 o'clock the following morning there was a recurrence of the hematemesis, after which for several days he had no gastric symptoms, pain or vomiting, but was extremely feeble and finally went to the hospital. The patient had never had any symptoms of ulcer, there was nothing to suggest precirrhosis or cirrhosis, heart disease, tuberculosis, etc., so Dieulafoy made a diagnosis of

"exulceration" After two days another severe hematemesis occurred, and since medical treatment had failed in the first case, it was decided to operate. When the stomach was opened, it was only after sponging the mucosa with the greatest care that a shallow exulceration, only as big as a dime, was seen. When lightly rubbed with a tampon, hemorrhage immediately appeared from a surface 2 inches (5 cm) in diameter. The bleeding section was infolded and sutured, the patient gradually recovered and several months later was in perfect health.

Dieulafoy appears to have considered these cases as identical, but Mayo Robson pointed out that they represent two different kinds of lesions. In the first case described, the lesion was more extensive and the surface layers were removed to such an extent that the arterioles running under the muscularis mucosae were exposed. In the second case there was a mere abrasion of the surface epithelium, which, though so small as to be scarcely perceptible to the naked eye, gave rise to the most severe hemorrhages. Mayo Robson stated that such abrasions may be overlooked post mortem, but, as seen when hemorrhage is going on, the mucous membrane seems to be studded with numerous bleeding points. However, in Dieulafoy's case it must be recognized that there was profuse bleeding from a fairly large area and that the epithelial abrasion was probably secondary to the hemorrhage.

### 3 HEMORRHAGE FROM A PORELIKE OPENING INTO ONE OF THE GASTRIC VESSELS

Smith<sup>5</sup> in 1902 described an unusual lesion which he claimed to have found in a number of cases. This was a small erosion, no larger than a pinhead, which did not spread superficially but led directly into an open vessel and could be detected only on the closest scrutiny. He reported a case as follows:

A woman, 22 years of age, was admitted to the hospital with a condition diagnosed as bleeding gastric ulcer, after having had two severe hematemeses. At operation, no ulcer was found, but in the mucosa there was a "villous looking patch" about the size of a quarter from which blood was oozing. The bleeding section was tied off by a purse-string suture, the patient at first did well, but later developed suppurative parotitis with edema of the glottis necessitating tracheotomy. She started vomiting blood again and died soon afterward. At postmortem examination it was noted that the old affected region was effectually sequestered, but near the pylorus was a small porelike opening into one of the gastric vessels with no trace to the naked eye of any ulceration, swelling or pathologic condition other than a simple solution of continuity in the mucous membrane.

### 4 HEMORRHAGE FROM MULTIPLE MINUTE EROSIONS

The condition known as "Einhorn's disease"<sup>6</sup> is characterized by multiple erosions of the inner surface of the stomach, which, however

<sup>5</sup> Smith, F. J. Gastric Ulcer, *M. Press & Circ.* **14** 539, 1902.

<sup>6</sup> Einhorn, M. Diseases of the Stomach, ed. 7, New York, William Wood & Company, 1929, p. 294.

bleed very little. If gastric lavage is performed when the patient is in a fasting state, one or more small pieces of mucous membrane are observed of a blood red color and about 0.3 or 0.4 cm. long and nearly as wide. Under the microscope, these fragments show well preserved glands and accumulations of red blood corpuscles. Only rarely is any blood noted, and this is usually when coughing spells occur during the lavage. The fragments partly or wholly peel off from the mucosa some time previous to the washing, which explains why there is no bleeding during the lavage. It is a question whether the exfoliations always take place at the same spots, the tissue constantly becoming replaced and peeling off, or whether most of the surface is affected to such an extent that small pieces of mucosa peel off here and there. Whether from the same spot or not, these exfoliations take place day by day in the stomach and effect temporary erosions. The chief symptoms are pain and a feeling of weakness. The pain is never intense, it occurs immediately after meals, is independent of the character of the food, persists for one or two hours and disappears gradually. Usually intervals of variable duration occur during which the patient is perfectly well. These patients are always treated medically, and the interior of the stomach has never been examined.

Aschoff<sup>7</sup> described a type of erosions, the so-called stigmas of Beneke, which are localized predominantly in the region of the greater curvature and may be so thickly scattered that countless small erosions are found. They are usually the size of a pinhead or slightly larger, only exceptionally reaching a greater diameter, and are of a peculiar wedge shape with a central loss of substance. They are found in all age periods and seem to have a definite relationship to nervous diseases. Beneke<sup>8</sup> expressed the belief that nervous arterial spasm causes small anemic necroses of the mucous membrane, followed by an injurious action of the gastric juice with digestion of the capillaries and hemorrhage. In some instances, the anatomic observations may be completely negative and the condition designated as "parenchymatous gastric hemorrhage." The ischemia is a transitory phenomenon and may be followed by hyperemia or normal circulation. Some authors have described a spastic contraction of the muscularis mucosae as the cause of the arterial blocking and the anemic necrosis, others find the cause more in constitutional, nutritional and circulatory disturbances. A summary of a case of this type reported by Jonas<sup>9</sup> follows:

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7 Aschoff, L. Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924.

8 Beneke, R. Ueber die hamorrhagischen Erosionen des Magens (Stigmata ventriculi), Verhandl. d. deutsch. path. Gesellsch. **12** 284, 1908.

9 Jonas, A. F. Operation for Ulcus Ventriculi Chronicum. Three Cases, with Remarks on Indications for Operation, West. M. Rev. **2** 285, 1897.

A German, 32 years of age, a butcher, married, had four sisters and six brothers. His father had died of stomach trouble of fifteen years' duration, and the oldest brother complained of gastric disturbances, the other brothers and sisters were well. The patient's illness had begun fifteen years previously with "cramps" in the stomach, lasting but a short time, and recurring at irregular intervals, most frequently in the summer. About three and a half years before admission to the hospital he began vomiting small amounts of blood, which from time to time increased in amount. All heavy foods, such as potatoes, bread and meat, caused "cramps," and he was obliged to discontinue the use of beer and wine because of the pain produced, which was usually relieved by emesis. During the last year emesis was not so frequent, but was much larger in quantity and consisted mostly of blood. Constipation was severe, requiring enormous doses of cathartics for relief. For more than two years he had been unable to work, for five months he had been almost constantly in bed, during the last four years he could lie only on his left side, and his weight had dropped from 200 to 130 pounds (90.7 to 59 Kg.)

On physical examination, the abdomen appeared rather full, with the greatest prominence about the umbilicus and a marked depression at the epigastrium. Peristaltic waves were very marked. Slight tapping on the left side of the umbilicus excited gastric peristalsis, which increased rapidly and produced pain sufficient to cause the patient to resume a sitting posture. The contents of the stomach were removed by a tube, there were almost 2 liters, the substance was a dark brown, with a coffee ground sediment, and contained undigested curdled milk and coagulated white of egg, which had been taken the night before. The empty stomach was filled with atmospheric air so that its outline might be distinctly traced, and seemed to fill nearly one-third of the abdominal cavity, its greater curvature filling the left hypochondrium and extending downward nearly a hand-breadth below and to the right of the umbilicus. The pylorus could be felt as an indurated mass. The abdomen was opened, and an incision parallel with the long axis of the pylorus showed that the lumen was pervious for an ordinary lead pencil, the pyloric wall was five-eighths inch (0.9 cm.) in thickness. The remainder of the stomach was not examined.

On the night of the fourth day after operation, the patient became restless and died suddenly. At autopsy, the stomach was enormously distended and contained nearly a gallon of bloody fluid with a large quantity of coffee ground material. After repeated examination, "a very large number of very small ulcers" were found in the hepatic end of the stomach together with innumerable small cicatrices, the former seat of ulcers. The pylorus was occupied by a dozen or more larger scars, and its wall was thickened with a mass of newly-formed connective tissue, but there were no recent ulcerations. All the other organs seemed normal. The immediate cause of death was given as renewed hemorrhage from the innumerable ulcerations.

The early history, the pyloric stenosis and the exaggerated gastric peristalsis would suggest a nervous origin in this case, the family history suggests a constitutional factor of some sort. Also, one wonders if in Einhorn's disease the interior of the stomach with its multiple tiny exfoliations might present an appearance similar to that described by Aschoff.

## 5 CAPILLARY OOZING

During the early years of the twentieth century, a number of eminent English physicians and surgeons<sup>10</sup> called attention to another type of condition, occurring in young women, in which although bleeding from the gastric mucous membrane had lasted for years, the most minute examination of the interior of the stomach might fail to show any lesion. It was stated that the essence of the disease was a liability to gastric hemorrhage independent of ulceration. The attacks of bleeding varied much in severity, being sometimes comparatively trifling but often severe, and at times extending over a period of many years with intervals of months or even a year or two between the attacks. These patients very often were or had been chlorotic and showed the symptoms variously known as "anemic dyspepsia," "chlorotic dyspepsia," etc. Hale White remarked that severe dyspeptic symptoms are commoner with chlorosis than with other anemias, and consist of hematemesis, persistent vomiting aside from the hematemesis and pain in the region of the stomach. These cases were often diagnosed as peptic ulcer, but the patients were not liable to the numerous serious complications of gastric ulcer. They might have been in perfect health at the time of the first hemorrhage and continued to look healthy, since there were fairly long intervals between the attacks. The prognosis was good, although relapses were frequent, the hematemesis was rarely fatal, and the attacks gradually ceased after 40 years of age.

In the following typical cases the interior of the stomach was actually examined.

A woman, 27 years of age, had a history of indigestion and pain after taking food for eight years. She had been in another hospital the year before for these symptoms. For the past two months the pain had been continuous and she had had occasional hematemesis to a small amount. On the day of admission, she vomited a pint of blood, on the following day, there was another hematemesis, and four days later another. She improved under medical treatment for one month, then had a recurrence of the symptoms followed in a fortnight by a return of the hematemesis. A month later, there was another attack of hematemesis. The

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10 White, W. H. Are Not Some Patients Said to be Afflicted with Gastric Ulcer Really Suffering from a Different Disease? *Lancet* **1** 1819, 1901. Herringham, W. P. A Lecture on Haematemesis, *Clin J* **27** 337, 1906. Dawson, Bertrand. The Diagnosis of Gastric Ulcer, *Brit M J* **2** 1032, 1905. Armstrong, G. E. The Wisdom of Surgical Interference in Haematemesis and Melena from Gastric and Duodenal Ulcer, *ibid* **2** 1087, 1899. Hood, D. W. C. Haematemesis, with Special Reference to That Form Met With in Early Adult Female Life, *Tr M Soc London* **15** 283, 1892. Mansell Moullin, C. W. Three Cases of Gastrotomy for Haematemesis, *Lancet* **2** 1125, 1900. The After History of Patients upon Whom Gastric Operations Have Been Performed, *Brit M J* **1** 1037, 1905. Robson, A. W. M. Discussion of the Surgical Treatment of Haematemesis, *Lancet* **2** 1626, 1902.

improvement seemed so slight that it was believed wise to operate. The stomach was turned practically inside out, but nothing was found to be the matter with it.

A woman, aged 33, was seized without premonitory symptoms with violent hematemesis, the hemorrhage recurred four days later and again three days following the second attack. The patient had been married three months, had been anemic and had had slight indigestion, but otherwise did not consider herself ill. Since the bleeding resisted the ordinary remedies, surgical intervention was advised. An incision was made in the axis of the stomach, and seven bleeding points were found in the mucosa. Two that were bleeding freely were taken up by artery forceps and the mucous membrane ligatured *en masse*, the others stopped on exposure to the air. A posterior gastro-enterostomy was performed. At the end of the second week, the patient was able to take solid food, and a year later had had no recurrence and was well in every respect.

A woman, 23 years of age, had pain, vomiting, hematemesis, a tender epigastrium and anemia, but no wasting. The first attack occurred in August, 1900, when she was in bed for two months, the second attack was in February, 1901, and lasted six weeks, the third attack occurred in January, 1902, and the fourth in July, 1904, at which time she was operated on. All that was found was a small oozing erosion on the posterior wall of the stomach, which was ligated. After the operation, there were many fresh hemorrhages and the patient's condition was not improved. A second operation was performed for another attack of hematemesis, but the attacks had continued until the case was reported.

Hale White stressed that in these cases the origin of the hemorrhage was not a local lesion, but that the blood oozed from multiple points in a mucosa that usually presented an unbroken surface. When minute erosions or ecchymoses were noted, he believed they were the result rather than the cause of the hemorrhage and were due to the blood tearing through the epithelial lining.

#### 6 "HEMORRHAGIC GASTRALGIA"

Closely associated with the chlorotic type, there were cases reported of older women with chronic symptoms, in whom the interior of the stomach showed "slight catarrhal inflammation," "congestion" or some other condition which seemed altogether inadequate to account for the serious nature of the bleeding. White proposed the name "hemorrhagic gastralgia" as being suitable for some of these.

The following case was originally reported by Thompson.<sup>11</sup>

A woman, aged 38, gave a classic history of gastric pain, epigastric tenderness, distress after eating and repeated attacks of hematemesis, with increasing weakness and emaciation, the symptoms lasting through many months. The patient had several serious attacks of hematemesis after admission to the hospital, and at the end of two weeks, since there was no improvement in her condition, the stomach was opened and the interior thoroughly explored with an electric

<sup>11</sup> Thompson, W. G. Hematemesis from Gastric Ulcer. Notes on Over Two Hundred Cases, *Am J M Sc* **130** 375, 1905.

light The mucosa appeared slightly granular and congested, but there was no cicatrix and no sign of any ulcer The incision was therefore closed and the patient died three days later from exhaustion following repeated vomiting

The first case we have to report is of this type

A woman, aged 38, was admitted to the Lankenau Hospital in May, 1922, with a history of indigestion and vomiting for eleven years, becoming progressively worse during the last three or four years and lasting from three to four days with intervals of one month between the attacks She experienced severe pain and belching of gas immediately after eating, occasionally vomiting or alkalis would bring relief Menstruation was regular, and she was never jaundiced She complained of headache all the time, which was worse during the attacks Two weeks before admission, she had diarrhea and melena with occasional expectoration of blood On physical examination, tenderness was noted in both the epigastric and the appendical regions Her teeth were in good condition, the lungs were clear throughout The temperature on admission was 99.6 F and varied while she was in the hospital between 98 and 99.4 F, with a pulse rate of from 80 to 104

The patient was operated on by Dr John B Deaver, and a chronically diseased appendix was removed The stomach was incised, the mucosa was congested, granular and oozed blood, but no trace of ulcer could be found She was given duodenal feedings for about five weeks, followed by a soft diet and milk by mouth

The relevant laboratory findings in this case were as follows The blood count showed 70 per cent hemoglobin, 4,000,000 erythrocytes and 18,700 leukocytes, with 83 per cent polymorphonuclears, 15 per cent lymphocytes and 2 per cent large mononuclears The urine was normal The phenolsulphonphthalein test gave 72 per cent elimination, with 45 per cent the first hour, 19 per cent the second and 8 per cent the third The blood sugar was 89 mg per hundred cubic centimeters of blood The Wassermann reaction was negative An x-ray picture of the gastro-intestinal tract showed no definite evidence of demonstrable pathologic change Gastric analysis by the fractional test meal was within normal limits

Since being discharged, the patient has communicated regularly with the follow-up department of the hospital The gastric pain persisted after the operation, though not so severe as before, and there were occasional attacks of vomiting but no hematemesis until October, 1924 In May, 1925, she experienced regurgitations of blood, in May, 1926, she vomited a large amount of "black material," and in December of that year she had an attack of vomiting of dark brown and black fluid The follow-up report for June 15, 1927, stated that the patient was quite well until March 1, when she started vomiting blood, she had been in bed off and on since then and had severe pains just after eating, but her general appearance was good From that time, although the gastric symptoms persisted, there was no hematemesis until November, 1929, when she vomited blood for two weeks with constant pain in her stomach made worse by the taking of food or fluid An x-ray picture of the stomach and duodenum made at this time was negative

The patient has continued in this state up to the time of writing this article Although the bleeding is not constant, it is persistent, and it may be assumed that during the attacks the condition in the gastric mucosa found nine years ago at operation is still present



In the literature there are reported numerous similar cases occurring in male subjects, two of which follow <sup>12</sup>

A man, 36 years of age, had suffered for several years from cardialgia and nausea. On July 5, he had a sudden profuse hematemesis, a diagnosis of gastric ulcer was made, and he was given treatment for ulcer for two months. However, gastric pain was constant throughout the summer, with frequent vomiting. On September 16 and 18, after test breakfasts, the laboratory reports showed a large amount of mucus, free hydrochloric acid and no organic acids. On September 22, the patient complained of severe pain in the stomach and vomited from 800 to 1,000 cc of nearly fresh blood. The stomach was opened, and systematic exploration revealed a superficial erosion 1 cm in size and three smaller erosions. All these points were ligated, the patient recovered and left the hospital on November 3. He had no further hemorrhages, but continued to suffer from gastralgia and a dilated stomach, which resisted all treatment.

A man, 28 years of age, had been in the hospital three times in three years for treatment of gastric ulcer. During the last admission, he had medical treatment for one month, but hematemesis, melena and hiccups persisted. At operation, exploration of the stomach and as much of the duodenum as possible was negative. A gastro-enterostomy with suture was performed. Vomiting continued after the operation, and the patient died on the fifth day. Postmortem examination showed a slight lesion of the mucosa 1 cm square, situated 4 cm from the pylorus, and general peritonitis.

#### 7 DIFFUSE BLEEDING AS A RECURRENCE AFTER OPERATION FOR ULCER

Diffuse bleeding may occur from the gastric wall from one to ten years after operation. Fitzgerald <sup>13</sup> reported the following case:

A man, a clerk, 34 years of age, who had been operated on for a perforated ulcer on the anterior wall of the duodenum, made a good recovery and was discharged "well." Almost seven years later, he was readmitted because of blood in the stool and a feeling of profound weakness, a second operation revealed half a dozen areas of hemorrhage in the mucosa of the stomach, but no ulceration, acute or old, could be found. Part of the stomach and the first part of the duodenum were removed, the patient recovered, and two years later was in excellent general health, with no indigestion and no hemorrhages.

The second case I wish to report seems to be of this type.

A man, 38 years of age, who was employed as a bank runner for a bond house, was admitted to the Lankenau Hospital four days after having had a sudden severe

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12 Andrews, E W, and Eisendrath, D N. On the Surgical Treatment of Hemorrhage from Gastric Ulcers, *Ann Surg* **30** 393, 1899. Lund, F B, Joslin, E P, and Murphy, F T. Operations upon Benign Diseases of the Stomach at the Boston City Hospital and Massachusetts General Hospital 1898-1903, inc, Boston M & S J **91** 113, 1904.

13 Fitzgerald, R R. Chronic Follicular Gastritis. With a Report of Nine Cases, *Brit J Surg* **19** 25, 1931.

hematemesis while sitting at dinner, without apparent cause and with no associated pain. He fainted and was carried to a sofa, and soon afterward the hematemesis recurred. He regained consciousness and except for exhaustion felt all right. He was advised to come to the hospital at once, but for three days went to his work as usual, during this time, the stools were black, but there was no gross bleeding from the rectum. On the fourth day, he fainted again and reported at the clinic.

He had had measles, whooping cough and scarlet fever with no complications in childhood and an appendectomy in 1916, but claimed to have been in good health until 1918, when he was gassed and wounded slightly in the elbow while in France. A few months later, while still in the army, he had bronchopneumonia, tuberculosis developed and he was in the hospital most of the year 1919. He then began to have pain in his stomach, which was fairly continuous and griping and was worse after meals, he vomited his food, but there was no blood either in the vomitus or in the stools. Most of 1920 was spent in a sanatorium, the pain in the stomach persisted, and jaundice with clay-colored stools developed. In 1921, hemorrhoidectomy and gastro-enterostomy for ulcer (?) were performed, after which the condition of the lung healed, the pain disappeared from his stomach and he had no vomiting, he seemed to be in good condition until January, 1926, when Dr. Deaver removed his gallbladder after one week of severe griping pain. Gallstones were present. A few months later he started vomiting again, usually about one hour after meals, with nausea but no pain, the vomitus consisted of mucus, bile and undigested food. From 1926 until February, 1931, when he was admitted to the hospital, he had had about nine such spells each year, he was ill for only a few hours, then recovered and felt quite well.

Physical examination revealed a tender area in the epigastrium, with increased resistance, and palpation in that region made him weak and nauseated. In the left lower quadrant a mass was palpable, which was soft, movable, smooth and tender and was said to feel like a spastic sigmoid. The heart was normal except for a very faint systolic murmur. Percussion revealed the lungs resonant throughout, slight impairment at the left apex posteriorly, no râles, normal breath sounds and decreased rhonchal fremitus posteriorly at the left apex, with a suggestion of whispered pectoriloquy.

The blood count, on many tests, showed erythrocytes, from 2,680,000 to 1,360,000, with from 50 to 30 per cent hemoglobin, and from 4,800 to 11,000 leukocytes, from 62 to 74 per cent neutrophils, from 16 to 31 per cent lymphocytes, from 5 to 8 per cent large mononuclears, from 1 to 2 per cent transitionals and 1 per cent eosinophils. The Wassermann and Kahn reactions were negative, the Gruskin test for carcinoma gave negative results. The urine was normal, all examinations of the feces were positive for blood, showing from a faint to a very heavy trace. An x-ray picture of the chest for foci of infection was interpreted as showing an old peribronchial infiltrate extending from both hili generally throughout both lungs. Both upper lobes, particularly both first interspace trunks, were cottony on their periphery, suggesting old localized lesions, but not sufficiently definite for a diagnosis of present activity.

From the history, it was thought that this patient had a marginal ulcer. He had previously been operated on for ulcer, and he had two classic attacks simulating perforation while he was in the hospital. He was given four transfusions of blood, but in spite of all therapeutic measures, he went into shock and died on the twelfth day after admission.

At autopsy, the lungs were negative for active tuberculous lesions, and in the stomach there was no ulcer or perforation as was expected, but in the mucosa

proximal to the perfect gastro-enterostomy were a large area of tiny petechial hemorrhages and a smaller similar area near the gastro-enterostomy. There was no evidence of ulcer in the gastro-intestinal canal and no scar in the duodenum. It seems doubtful that the patient ever had an ulcer.

Several types of gastric bleeding have been described, all of them probably etiologically distinct from those listed in the foregoing tabulation, namely

- 1 Diffuse gastric hemorrhage due to physical or emotional strain
- 2 Profuse hemorrhage from superficial defects in the mucosa

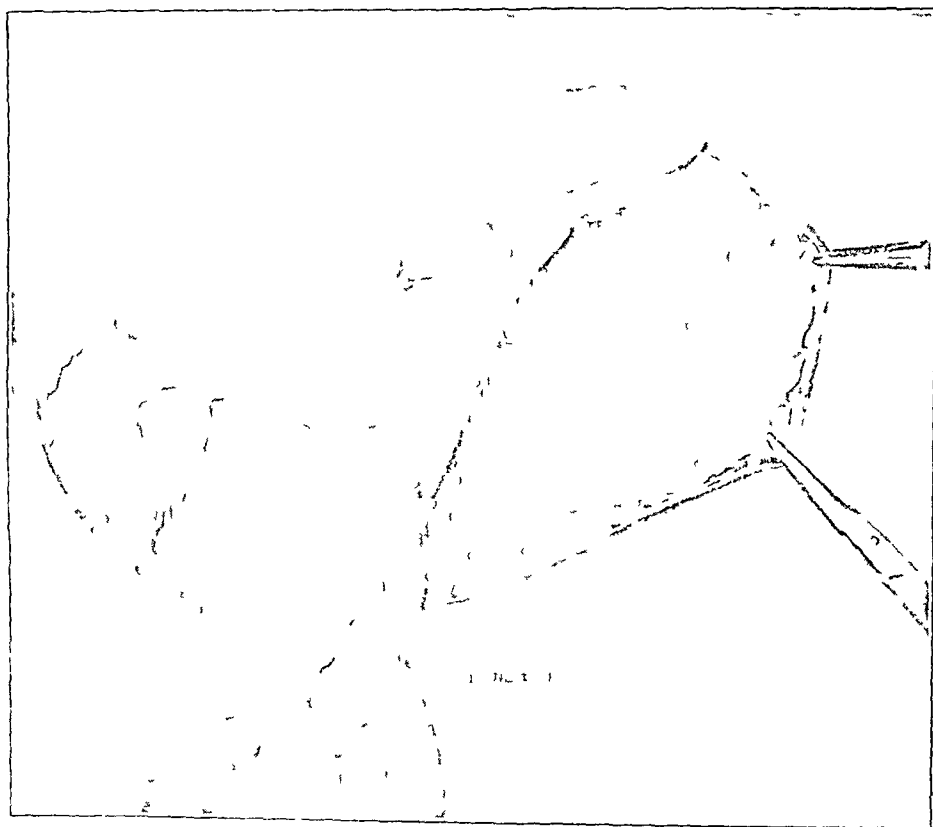


Fig 3—The numerous minute bleeding points from which hemorrhage sufficient to cause a fatal issue took place

- 3 Hemorrhage from a porelike opening into one of the gastric vessels
- 4 Hemorrhage from multiple minute erosions
- 5 Capillary oozing
- 6 "Hemorrhagic gastralgia"
- 7 Diffuse bleeding as a recurrence after operation for ulcer

In the accompanying table are listed thirty-six additional cases, in each of which the stomach was opened and the mucosa carefully examined

*Observations in Thirty-Six Additional Cases*

Age	Sex*	Comment	Result	Reported by
	♀	Hematemesis for 1 month to the extent of 30 ounces, mucosa showed several losses of substance so shallow and velvety they were not strikingly different from rest of stomach	Death	Abbe (New York M J 53 519, 1891)
35	♀	Copious hematemesis for 7 days, good previous health, no symptoms of ulcer, mucosa showed oozing from 3 points, resembling linear fissures in 2 cases and stellate fissure in third, around fissures over area of 1 cm was an apparent loss of epithelium	Complete recovery	Armstrong <sup>10</sup>
31	♀	Indigestion and pain 2 years with repeated vomiting of small quantities of blood, no ulcer found in stomach all symptoms except hematemesis recurred after operation	Recovery	Rodman (Philadelphia M J 5 1302, 1900)
27	♀	Epigastric pain and vomiting 8 years about 1 hour after eating, hematemesis at 3 and 4 year intervals, and monthly for 5 months before admission, several small points oozing blood and at cardiac end an area 2 inches square on the anterior wall	Good recovery	Rodman (Philadelphia M J 5 1302, 1900)
36	♀	Sausage poisoning 2 years previously, repeated gastric hemorrhage, vomited all solid food, circular constriction about pylorus and stomach dilated, no ulceration	Recovery	Rodman (Philadelphia M J 5 1302, 1900)
29	♀	Epigastric pain for 3 years ½ hour after eating, 18 months previously vomited coffee ground material, 2 days previously hematemesis, 4 ounces, and constant hematemesis from that time, physical examination negative except for localized tenderness in epigastrium, mucosa showed several areas oozing blood	Death	Lund, Joslin and Murphy <sup>12</sup>
23	♀	Previous history unimportant, 36 hours before admission vomited blood and showed melena, repeated 3 times, 2 small bleeding areas near incision probably due to trauma, but no evidence of ulceration	Death	Lund, Joslin and Murphy <sup>12</sup>
21	♀	Every symptom of gastric ulcer with repeated hematemesis and characteristic pain, interior of stomach showed slight catarrhal inflammation	Death	Hale White (Lancet 2 1189, 1906)
21	♀	Sudden severe hematemesis with recurrences developed parotitis and died of hyperpyrexia, no source of bleeding in esophagus, stomach or bowel	Death	Hood <sup>10</sup>
25	♀	Pain, vomiting, hematemesis, stomach opened, no visible pathologic changes	Complete recovery	Hood <sup>10</sup>
34	♀	Severe hematemesis and melena, no history of dyspepsia or vomiting after food, abdomen not tender, one very small area oozing blood on posterior wall near pylorus	Recovery	Mansell Moullin <sup>11</sup>
37	♀	Gastric pain, vomiting and hematemesis for 7 years, died in midst of hemorrhage, careful search failed to show any source for bleeding, stomach sent to museum	Death	Hale White (Lancet 2 1189, 1906)
	♀	Pain, vomiting and hematemesis for years, no source of bleeding or ulcer in stomach	Excellent recovery	Hale White (Lancet 2 1189, 1906)
41	♂	Pain in epigastrium not related to food, vomiting, copious hematemesis, melena, well 2 years and had recurrence with more persistent hematemesis, 4 pinpoint hemorrhages near pylorus	Death	Hale White (Lancet 2 1189, 1906)
30	♀	Periodic pain and vomiting after food for 12 years, 3 years previously had profuse hematemesis, small abrasion from which blood was oozing, no return of hematemesis after operation, but pain and vomiting continued	Recovery	Dawson <sup>10</sup>

\* In this column, ♂ indicates male, ♀, female

*Observations in Thirty-Six Additional Cases—Continued*

Age	Sex*	Comment	Result	Reported by
28	♀	Skin tenderness and deep tenderness in epigastrium, pain, vomiting, hematemesis, recurrent symptoms for 11 years, congested patch of mucosa	Recovery	Dawson <sup>10</sup>
28	♀	History of acute gastric pain, hematemesis, melena stomach appeared normal, cause of death could not be determined	Death	Thompson <sup>11</sup>
31	♀	Good previous health, "indigestion" for 14 days, hematemesis day previously, and severe hematemesis on day of admission, at operation, stomach turned more or less inside out, mucosa deep red all over and seemed to bleed wherever it was touched, patient died of shock, at autopsy, slight erosion seen at cardiac end in middle of which was a small opened vein with a thrombus formed in its lumen	Death	Herringham <sup>10</sup>
26	♀	In hospital 8 years previously for gastric pain and vomiting well 2 years hematemesis, bleeding points in stomach found and ligated 8 weeks after operation severe hematemesis and another later	Recovery	Herringham <sup>10</sup>
54	♀	For many years had abdominal pain, vomiting and dyspepsia, hematemesis after admission and 10 days later severe and fatal hematemesis, no ulcer, erosion or bleeding point found in stomach or intestine, the mucous membrane of which appeared quite healthy	Death	Hale White (Lancet <b>2</b> 1189, 1906)
44	♀	Indigestion 25 years, sudden hematemesis and melena, repeated soon after, did not feel ill but had some epigastric pain, 3 small bleeding points at commencement of duodenum craterized and arteries of greater curvature ligated at autopsy, stomach and duodenum appeared absolutely normal	Death	Hale White (Lancet <b>2</b> 1189, 1906)
18	♂	Strong, healthy with unimportant previous history, suddenly vomited 2½ pints of blood and melena, 5 days later vomited 1½ pints, 5 days after that 1 pint, patch on posterior wall oozing blood from a few minute points and slightest touch produced further hemorrhage anywhere in area, mucosa otherwise normal	Death	Hale White (Lancet <b>2</b> 1189, 1906)
19	♀	Pain after eating for several weeks, vomited large quantity of blood, 4 recurrences in 12 hours, operation showed no ulcer	Recovery	Hale White (Lancet <b>2</b> 1189, 1906)
47	♀	Stomach and duodenum explored for ulcer but none found, posterior gastrojejunostomy satisfactory, but condition not improved, still had hematemesis and melena, but these disappeared if kept in bed and put on milk diet	Recovery	Hale White (Lancet <b>2</b> 1189, 1906)
33	♀	Pain and vomiting for 4 years with hematemesis once no ulcer or scar in stomach gastrojejunostomy, symptoms returned 5 months later and persisted, postoperative hematemesis once	Recovery	Mansell Moullin <sup>10</sup>
24	♀	Pain, vomiting and hematemesis for 4 years, looked quite healthy, mucosa carefully examined, but appeared perfectly healthy blood count 5,400,000, with normal hemoglobin	Recovery	Mansell Moullin <sup>10</sup>
32	♀	For several years had pain in stomach many attacks of hematemesis during 9 months, looked quite healthy, interior of stomach and duodenum thoroughly explored, no abnormality seen	Complete recovery	Hale White (Lancet <b>2</b> 1189, 1906)
23	♀	Cramps in stomach for some time, sudden copious hematemesis and melena, small erosion traversed by open arteriole	Death	Dieulafoy <sup>4</sup>
20	♀	Excellent previous health and good constitution, sudden violent hematemesis and melena very superficial erosion in mucosa with open arteriole	Death	Dieulafoy <sup>4</sup>

\* In this column, ♂ indicates male, ♀, female

*Observations in Forty-Six Additional Cases—Continued*

Age	Sex*	Comment	Result	Reported by
30	♀	Sudden hematemesis, superficial loss of substance in mucosa	Death	Diculafox <sup>4</sup>
35	♂	Gastric pain for several months, expectorated few streaks of blood and short time later died without even vomiting, 2 liters of blood in stomach and ecchymotic spot found near cardia	Death	Diculafox <sup>4</sup>
	♀	Three or four stellate ecchymoses from 1 to 2.5 cm in diameter found in mucosa, one containing small eroded arteriole	Death	Diculafox <sup>4</sup>
39	♀	Repeated attacks gastric pain, vomiting, hematemesis, in hospital on 3 separate occasions for gastric ulcer last attack lasted 10 weeks, at autopsy, no obvious sign of disease could be detected in mucosa	Death	Hale White (Janet 2 1189, 1906)
42	♀	Recurrent hematemesis 6 years at intervals of about 6 months, vomiting 2 hours after food followed by severe pain for from 1 to 2 hours, tender epigastrium and pain below angle of left scapula, 11 children, 6 living not markedly anemic and nothing important in history or general condition 2 small superficial ulcers at cardiac end involving only mucosa and bleeding freely when touched	Complete recovery	Mansell Moullin <sup>10</sup>
42	♂	Five years previously had pain after food vomiting, loss of weight, well until 7 months before admission, when old symptoms recurred with hematemesis and melena, stomach very large, mucous membrane was closely folded on itself and showed area 1½ inches in length from which blood was pouring freely, surface of lesion irregular and covered with granulations, edges well defined but not steep only mucosa involved, bleeding area infolded and sutured and patient left hospital apparently perfectly well	Complete recovery	Mansell Moullin <sup>10</sup>
51	♀	Continuous dyspepsia with 2 attacks of hematemesis, slight dilatation of stomach with recent erosion at cardiac end, anterior gastrojejunostomy performed, after operation complained of a "slight rather heavy feeling after meals," was ill on an average of once in 3 months but had no hematemesis and general health was better	Recovery	Mansell Moullin <sup>10</sup>

\* In this column, ♂ indicates male, ♀, female

The following list of complaints in diffuse gastric bleeding was brought out by an analysis of fifty-two cases, but this list is typical also of the chief complaints offered by patients in whom the underlying lesion is proved to be a peptic ulcer, cholecystitis, appendicitis, gastrointestinal allergy and a number of other diseases

*Chief Complaints in Fifty-Two Cases of Diffuse Gastric Bleeding*

- 1 Hematemesis, single or recurrent, profuse or moderate, with or without symptoms of shock
- 2 Gastric pain (cardialgia, gastralgia)
- 3 Epigastric tenderness
- 4 Distress after eating (a sense of weight or fulness)
- 5 Chronic indigestion (one to twenty-five years)
- 6 Nausea
- 7 Vomiting

- 8 Hiccups
- 9 Flatulence
- 10 Melena
- 11 Constipation
- 12 Headache

## ETIOLOGY AND PATHOGENESIS

The stomach is a very busy organ, muscularly, vascularly, nervously and digestively. The magenstrasse, or muscular trough of the lesser curvature along which course food in its passage seems to offer the greatest friction is the usual situation for local lesions, but in diffuse bleeding the hemorrhage may arise from any part of the stomach. Pringle,<sup>14</sup> in describing hematemesis during attacks of urticaria, said "The fact that the capillaries of the gastric mucosa form an extremely fine and extensive network supported and separated from the cavity of the organ only by a delicate basement membrane and a single layer of columnar epithelial cells fully accounts for the occurrence of hemorrhage and for its amount in the more severe attacks."

Nevertheless, Hale White concluded that the cause of oozing from an intact gastric wall in the absence of any definite inciting factor is obscure. Since there is no striking increase of blood pressure, the change must be in the walls of the vessels and is local in the stomach as no bleeding takes place at distant parts of the body. Surgeons who have seen the oozing of blood during life have stated that it closely resembles the oozing from the uterus during menstruation. Thompson believed that these cases of diffuse gastric bleeding suggest those of early hemoptysis without discoverable bronchial ulceration and the early hemorrhage of typhoid fever which arises during the congestive stage before the ulcers are well defined, they also resemble the cases of hematemesis that result from congestion in chronic endocarditis and hepatic cirrhosis with portal obstruction, yet no such lesions are found to explain them.

Hood spoke of a section of North Devon where anemia was a common form of illness among the young women. Gastric hemorrhage, in many cases very profuse, frequently accompanied the illness, and the hemorrhage was regarded as a part of the anemia due to the change in the blood. It was noted that in many cases, previous to the hemorrhage, an extreme state of constipation existed, and that the patients made a rapid recovery when treated with iron and sulphate of magnesia. Autopsy was performed in a case in which the hematemesis was fatal, and the wall of the stomach was found to be intact.

One still sees an occasional reference to "vicarious menstruation" in connection with most every type of diffuse hemorrhage. One of the

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<sup>14</sup> Pringle, J. J. On a Case of Recurrent Haematemesis with Urticaria, *Tr Clin Soc London* **18** 143, 1885

English authors has pointed out that the term "vicarious" is ill advised, because what is meant is simply an extension of the range of the disturbance in the uterus

It has also been suggested that periodic oozing from the gastric mucosa may be a process of the same kind as that found in cases of epistaxis in which there is a recurrent oozing of blood from the nasal mucous membrane

In cases in which there is persistent vomiting over a period of many years, the hematemesis is quite probably the result of the vomiting. Aschoff stated that the act of vomiting is introduced by hyperemia of the abdominal organs and particularly of the stomach. Then follows the compression of the abdominal contents by the abdominal musculature, and finally the active contraction of the stomach itself. The pyloric canal is tightly closed while the fundic portion is undergoing the vomiting motions. Consequently, two factors, blood engorgement and spasmodic contraction, act together in producing a venous stasis hyperemia and a venous hemorrhage on the summits of the fold system. That the venous stasis hyperemia, as such, can actually lead to typical hemorrhages and hemorrhagic erosions has been proved by many experiments. Aschoff believed, however, that although venous stasis might be primarily responsible for erosions of the fundus, particularly in vomiting and asphyxia, arterial anemic necroses also might arise from various cramplike conditions of the stomach.

When the hematemesis is due to increased intra-abdominal pressure or to mental excitement, since the patients are normally in good health one can surmise a constitutional fragility of the walls of the vessels.

In studying his series, Dieulafoy found the case of a man who had never had gastric symptoms but who was taken with sudden severe hematemesis and died. At autopsy, three lesions were found on the lesser curvature of the stomach, the middle one was a fully developed chronic ulcer in the crater of which was a sectioned arteriole completely obliterated by a fibrinous clot. On either side was a superficial erosion, one of which was traversed by a vessel with a lateral opening that was visible with the microscope. Since the entirely sectioned vessel in the old ulcer was obliterated by a clot, it seemed that the fatal hemorrhage came from the vessel traversing the superficial lesion, and Dieulafoy believed that here might be the evolution of a gastric ulcer in its confirmed state and in the initial stage of a superficial erosion.

Konjetzny,<sup>15</sup> after a minute examination of more than 500 resected specimens, concluded that the typical ulcer of the stomach and duodenum begins as an erosion of the mucosa, and that the erosions are

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15 Konjetzny, G. E. The Inflammatory Basis of the Development of Typical Ulcer of the Stomach and Duodenum, *Ergebn d inn Med u Kinderh* 38 184 1930



the result of gastritis Konjetzny believed that in his material there was evidence of all stages of development from the initial erosion to the chronic form, and he distinguished stages of gradual transition between inflammatory erosions and acute ulcer

Spira<sup>16</sup> has recently pointed out again that there are two distinct forms of ulcer, acute and chronic, which are etiologically independent of each other, and that the exulceratio simplex of Dieulafoy is an acute ulcer showing all the signs of some toxic or acute infective cause Lesions of this type are uncommon, sudden, virulent, of short duration fatal or rapidly healing, with no local inflammation and no hyperchlorhydria and are essentially of systemic origin In chronic ulcers, the appearance of inflammation is early and persistent, it is present as a preulcerative condition, the ulcer being only an ultimate stage of the mechanism which induces the inflammation and representing the point of its greatest intensity

Einhorn stated that in the majority of his cases chronic gastric catarrh was probably the cause of the erosions, although at times there might have been some undeterminable factor, and that one would imagine that cases of this type would present a fruitful soil for the development of ulcers This, however, does not seem to be the case for in none of these patients was there any justifiable supposition of an existing ulcer during the long course of their illness

It is well known that chronic gastric ulcers are almost without exception found in the region of the lesser curvature, while the various superficial lesions previously described are all located in the fundus Aschoff explained that although mucous erosions may occur in any part of the stomach, owing to the anatomic-functional structure the fate of a loss of substance in the mucosa of the gastric pathway must be quite different from that of an erosion of the fundus The gastric pathway and the pyloric canal may be conceived of as a sort of functional entity with the rest of the stomach representing another entity The gastric pathway extends from the cardia to the beginning of the pylorus, where it spreads out superficially and goes over into the pyloric canal, and is limited by four taut longitudinal folds of mucous membrane It possesses its own muscle system and receives its blood supply only through the recurrent branches of the gastric or pyloric arteries The fundus, on the other hand, receives blood from the arterial branches of the right and left gastric epiploic arteries and also from collateral branches of the gastric artery Ligations in the region of the gastric epiploic arteries have no recognizable influence on the mucosa of the fundus, while ligations of the gastric or pyloric arteries, or of both vessels, lead to localized nutritional disturbances of the mucosa Also,

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<sup>16</sup> Spira, J Jacques The Causation of Chronic Gastro-Duodenal Ulcers A New Theory, London, Oxford University Press, 1931

the fundus presents a complicated mass of folds in close approximation, the mucosa is much thicker, and by contraction of the muscularis mucosae is made still thicker. The mucosa of the fundus shows a remarkable tendency to produce, through metaplastic processes, a sort of thin mucus which is poured out over the surface of the wound, and there is a greater tendency to epithelization and granulation. It happens then, that defects in the fundus are quickly covered by a sort of protecting membrane, while defects of the gastric pathway lie bare; in the fundus, there is the greatest mobility of the fold system, in the gastric pathway, there is taut longitudinal stretching, in the former, there is discharge of the gastric juice, in the latter, its reception as by a drainage tube. Therefore, defects along the gastric pathway show a more intense reaction than those in the fundus, continue gaping in a quite different manner, come into contact with gastric juice much longer and are more likely to be injured mechanically by the peristaltic motions than is possible in the region of the fundus, all of which would seem to favor the development of a chronic ulcer. Aschoff stated, however, that all manner of superficial erosions may arise under the influence of disturbed gastric function and concluded that the various anomalies of the gastric mucosa have nothing to do with the typical gastric ulcer, but are the result of the most varied diseases of the stomach.

It seems likely that, even in normal persons, a metabolic upset will cause temporary abrasions of the epithelium or losses of substance in the gastro-intestinal tract, similar to those found in the mucous lining of the mouth, and that ordinarily these heal spontaneously, but, when occurring in the stomach with its intricate structure and great activity, they may at times be more serious. Konjetzny found erosions similar to those in the stomach in parts of the intestinal tract which are inaccessible to the action of the gastric juice.

At present, there is a tendency to consider anaphylaxis or food allergy as a possible cause of gastric disturbances, and it is a question whether gastro-intestinal allergy might not be a factor in the production of some of the conditions under discussion, since where the attacks are recurrent they appear allergic in character. Pottenger<sup>17</sup> explained the anaphylactic state as follows:

There occurs at times an incomplete elaboration of protein, which results in unmetabolized products gaining access to the blood and lymph streams, from which they are deposited in the skin and mucous membranes. These products possess the property of sensitizing tissues, and particularly of producing their effects upon the parasympathetic neurocellular mechanism. When the substances which have sensitized the cells again come in contact with them a reaction of hypersensitivity occurs. Such a reaction may appear as a vaso-motor rhinitis, an asthma, a hay fever, a

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<sup>17</sup> Pottenger, F. M. The Potential Asthmatic, *J. Lab. & Clin. Med.* **13** 913 1928.

severe gastro-intestinal disturbance, an urticaria, an eczema, a colloidoclastic reaction, or other syndromes which are less easily recognized. Certain individuals who are prone to this condition seem to possess also a constitutional hepatic inadequacy which is of great importance because of the detoxicating influence of the liver upon substances of alimentary origin. Such individuals show idiosyncrasy to foods and suffer from anaphylactic states more often than those with normal liver function.

Eppinger and Hess<sup>18</sup> expressed the belief that in such patients there is, primarily, a "vagotonic disposition," that is, an abnormal irritability of the parasympathetic nervous system.

In studying the present series of cases, one must agree with these authors that the "neurology of the viscera" is to be considered. A mucous membrane closely folded on itself (case 35, table 1) is regarded as an indication of nervous overactivity, the persistent vomiting, the pylorospasm, the hiccups and many of the other symptoms may be manifestations of a dysfunction of the vegetative system. In this connection, Pottenger stated that nerve action depends on the degree of alkalinity or acidity and on the physical state of the cell and its content, as well as that of the surrounding fluids, in substances such as nutritive materials, cholesterol, hormones and various electrolytes such as calcium, sodium, potassium, phosphate and magnesium. The vagus nerve is closely associated in its action with the potassium of the cell as opposed to the sympathetics, which are linked up in their activity with the calcium of the cell. With a predominance of the vagus, therefore, would go a deficiency of blood calcium with an excess of blood potassium and an increase of blood phosphates. With the present understanding of calcium metabolism, it seems logical to suppose that there is a calcium deficiency in some of these patients.

#### DIAGNOSIS

The diagnosis of hemorrhage, *per se*, is self-evident, but determining the point of origin of the hemorrhage, whether it is local from an esophageal varix, a peptic or marginal ulcer, a polypus or carcinoma or diffuse bleeding, is always perplexing. The presence of an esophageal varix is usually accompanied by other manifestations of cirrhosis. Carcinoma with its resultant cachexia, anemia and general dissipation of the body integrity is too well known to warrant further discussion. The necrosis and angry congestion of the mucosa provoked by ingestion of poisonous substances, such as mercuric chloride, lye, iodine, etc., need not be discussed. However, polypi may exist without clinical evidence. Patients with gastric ulcers, also, only occasionally produce the famous recurrent symptom-sequence of pain, food, comfort or dis-

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<sup>18</sup> Eppinger, H, and Hess, L. *Vagotonia. A Clinical Study in Vegetative Neurology*, Washington, D. C., Nervous & Mental Disease Publishing Company, 1915.

persion of the pain by alkalis, that is to say, relief when the gastric acid is neutralized and the viscus is moderately filled, which phase is followed by more burning and indigestion when the food passes beyond the area of the ulcer and the alkalized phase is followed by an acid phase. One must keep in mind the important fact that peptic ulcer may exist and progress even to perforation without symptoms.

Thompson among a large series of cases exhibiting hematemesis, found three in which there was either no visible pathologic change or diffuse punctate hemorrhage, but no sign of ulcer and no scar. He stated that diagnosis of the exact condition is difficult as between hemorrhage from a circumscribed ulcer, which may be cured by operation, and that from a generally congested mucosa, which may not be so cured. In none of his large series of cases of hematemesis from all causes did the chemical analysis of the gastric contents prove of determining value because the results were too variable, not rarely in the same patient on successive days ranging from anacidity to hyperacidity. Additional difficulty was encountered in the variability and inconstancy of all the so-called "cardinal symptoms" and in the fact that any one symptom, such as pain, vomiting or tenderness which had been present steadily for a long time, might spontaneously disappear or give place to another.

Hale White stated that points that will help in separating cases of diffuse bleeding from those of gastric ulcer are that the former are almost confined to women, the patients are likely to be less wasted than the sufferer from gastric ulcer, and although some give a history of chronic dyspepsia, pain after the ingestion of food and epigastric tenderness, the dyspeptic symptoms are probably less severe. The occurrence of fairly long intervals during which there is no complaint of gastric symptoms is on the whole in favor of diffuse bleeding.

Clerf (personal communication), by gastroscopic examination, observed infiltration and thickening of the mucous membrane with what appeared to be superficial erosions in a case in which there was no definite ulceration, there was slight bleeding from the erosions. Gastroscopy, therefore, may be of use in making a diagnosis, although it has not proved of much practical value.

#### *Principal Diagnostic Factors in Diffuse Bleeding*

- 1 It occurs in young adults (from 20 to 40 years)
- 2 There is a predominance of females over males (approximately 4:1)
- 3 The evolution may be silent, or nearly so, with hematemesis the first symptom
- 4 The patient may have had good previous health with no gastric symptoms
- 5 There may be a period of several months or a year or more between attacks
- 6 The condition may be present as a recurrence after operation for gastric or duodenal ulcer
- 7 The symptoms are probably less severe than those in cases of true ulcer
- 8 The x-ray picture of the gastro-intestinal tract is usually negative

9 Gastroscopy may be of value in determining the type of lesion

10 Very often, subsequent to the hemorrhage, all pain and discomfort cease, which could hardly be the case if active ulceration were in progress

In cases with sudden profuse hematemesis, an immediate differential diagnosis between local or diffuse bleeding of an ulcerating or non-ulcerating process is of secondary importance, except that surgeons would be more hesitant in the presence of diffuse hemorrhage. But, when the underlying pathologic condition is a temporary erosion or a comparatively benign capillary oozing, the general treatment would be different from that in a case of gastric or duodenal ulcer. Smith believed that mucous erosions are common, but that the stomach will heal from erosions as rapidly as the throat will heal from congestion, and that in three or four days the danger is probably past. It is important, therefore, when dealing with gastric bleeding, to keep in mind the various types of conditions that may be present in the mucosa and give rise to alarming hemorrhage, namely slight catarrhal inflammation, congestion, slight granulation, capillary oozing, petechiae and ecchymoses, abrasions of the epithelium and mucous erosions.

#### TREATMENT

The treatment for profuse gastric hemorrhage may be divided into three stages. The first stage is the immediate treatment for shock, and since a differentiation between local and diffuse bleeding from the stomach is practically impossible, the therapy for both conditions is the same. The patient must be kept at absolute rest by means of morphine hypodermically, ice being applied to the abdomen and heat to the extremities. The lower bowel should be washed out, and for forty-eight hours no attempt to furnish nutrition should be made. The matter of transfusions is a moot question, as the great majority of gastric hemorrhages cease of their own accord. The red blood count may fall as low as 750,000. It is our practice to type all patients for transfusion promptly, and when the blood count falls below 1,000,000 with the patient's general condition becoming more serious, to give from 300 to 500 cc of citrated blood.

The various hemostatic serums should be tried, although cessation of bleeding following their use is exceptional rather than the rule. The procedure that stops hemorrhage in one patient may fail in the next. In my experience, a liquid extract of the plant *Ceanothus americanus*, from 1 to 2 teaspoonfuls three or four times a day, and an extract of *Capsella bursa-pastoris*, 15 drops three times a day, have most frequently proved effective. Normal horse serum and the patient's own serum in small doses of from 2 to 10 cc are at times effective.

Soper,<sup>19</sup> in a recent article, advocated the treatment of gastric hemorrhage by the retention catheter introduced intranasally. The stomach is lavaged with cool tap water by means of a large glass piston syringe, and the tube is left in the stomach in order that a recurrence of the bleeding may be immediately detected and all acid secretions withdrawn. On the fifth day, the tube may be allowed to pass down into the duodenum and a high caloric mixture of milk, egg and lactose given with gelatin water and egg albumin water by mouth.

Operative intervention would appear to be an unwise procedure at this stage, Mayo Robson stated that the treatment of parenchymatous or capillary hemorrhage by any surgical method would seem to be of doubtful value. A limited personal experience and information obtained from the literature point to the conclusion that mechanical interference is not of necessity fatal, but it is agreed that the patients stand a better chance of recovery without rather than with operation,

After the bleeding has stopped, attention to the nutrition and elimination is indicated. Duodenal feedings for several days through the Jutte tube have proved invaluable in tiding the patients over a precarious period when the margin between success and failure in the establishment of substantial up-building is so narrow.

In cases in which it seems likely that the bleeding has been diffuse rather than from a chronic circumscribed ulcer, the subsequent treatment should be administered, keeping in mind that many of the lesions heal spontaneously and that an excessive use of drugs in general should be avoided. Adequate nutrition, with liver extract and iron to stimulate blood regeneration, is essential. All foci of infection should certainly be removed, and the patients may with wisdom avoid undue physical and mental strain. Adequate periods of rest are splendid for recuperation.

When indicated, atropine, from 1/200 to 1/50 grain (0.00032 to 0.0013 Gm.), three times a day, may be given to minimize the gastric acidity and also to counteract any tendency to pyloric spasm. Yet it has been stated<sup>7</sup> that all artificially produced defects in the gastric mucosa heal less quickly in the presence of atropine therapy, doubtless due to the loss of tone of the whole stomach. Colloidal hydrate of aluminum rather than sodium bicarbonate should be given to neutralize excess acid, since the former does not produce a subsequent hyperacidity. Calcium gluconate, from 10 to 30 grains (0.65 to 1.95 Gm.), three times a day by mouth, and parathormone injected subcutaneously twice weekly are valuable when there is a calcium deficiency, and finally the patients should have proper sedation for neurosis in the form of elixir of phenobarbital and elixir of bromide combined.

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<sup>19</sup> Soper, H. W. The Treatment of Hematemesis by the Retention Catheter, *J. A. M. A.* **97** 771 (Sept 12) 1931.

## SUMMARY

Serious gastric hemorrhage may occur from any part or all of the gastric mucosa either in patients who have had an irrelevant history and have apparently been well until a serious attack of hematemesis occurred, or in those who have suffered periodically from indigestion. Cases have been cited in which the gastric bleeding appeared to result from factors such as an increased abdominal tension, emotional strain, vagotonia, allergies, anemia, etc.

A differential diagnosis may be impossible, and in the majority of cases the diagnosis made before operation has been bleeding ulcer.

The treatment should be along medical rather than surgical lines, since hemorrhage of a diffuse kind arising from the gastric mucosa does not appear amenable to surgical approach. Support, elimination and rest are the cardinal features in the management of these cases.

# USE OF LIVER EXTRACT INTRAVENOUSLY

## REPORT OF TEN CASES

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Castle and Taylor<sup>1</sup> have recently shown that maximal responses of reticulocytes were obtained in the treatment of patients with pernicious anemia, during relapse, when the amount of liver extract derived from 100 Gm of liver was administered intravenously. The solution suitable for intravenous injection was prepared by dissolving approximately 4.5 Gm of a commercial preparation of fraction G<sup>2</sup> (liver extract) in physiologic solution of sodium chloride after washing the extract in ether. The solution was then filtered or centrifugated, sterilized by boiling for five minutes and made so that 20 cc contained the amount of material derived from 100 Gm of whole liver.

In studying the nature of the active principle in liver, Cohn<sup>3</sup> and West<sup>4</sup> and their respective associates had previously prepared highly purified fractions of liver which were suitable for intravenous injection and which were found to be potent. The practical application of these fractions was precluded because of the technical difficulties involved in their preparation and because of the large amounts of whole liver required (from 25,000 to 8,000 Gm).<sup>1</sup>

The maximum reticulocyte responses produced by these highly purified fractions were no greater than those obtained from a single intravenous injection of an amount of liver extract derived from 100 Gm of liver, therefore, Castle and Taylor demonstrated that there was a great loss in potency resulting from the subsequent stages of

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1 Castle, W B, and Taylor, F H L. Intravenous Use of Extract of Liver, *J A M A* **96** 1198 (April 11) 1931.

2 Cohn, E J, Minot, G R, Fulton, J F, Ulrichs, H F, Sargent, F C, Weare, J H, and Murphy, W P. The Nature of the Material in Liver Effective in Pernicious Anemia, *J Biol Chem* **74** 1414 (July) 1927.

3 Cohn, E J, McMeekin, T L, and Minot, G R. The Nature of the Substance Effective in Pernicious Anemia, *Tr A Am Physicians* **45** 343, 1930.

4 West, Randolph, and Howe, Marion. Liver Fractions in Pernicious Anemia, *J Clin Investigation* **9** 1, 1930.



chemical purification. Also, the reticulocyte responses produced by 100 Gm of liver extract given intravenously were as great as those obtained when large doses of liver extract no 343, N N R, were given in single or divided doses. That there was a defective absorption of the active principle contained in liver from the intestinal tract seems to be clearly demonstrated by them. They suggest that the strikingly greater effectiveness of the active principle when administered intravenously is possibly of some significance in the etiology of the disease and indicates that there may be a defect in the absorption of the hematopoietic factors contained in the food ingested.

More recently, Strauss, Taylor and Castle<sup>5</sup> have obtained satisfactory reticulocyte responses when a preparation similar to the one previously described was administered intramuscularly. Working independent of Castle and his associates, Prof M Gansslen<sup>6</sup> has reported similar results following the daily intramuscular injection of a liver extract.

A preparation suitable for injection purposes and made from liver extract no 343, after the method employed by Castle and his associates (as previously described), has been used intravenously by us in the treatment of ten patients. Seven of the patients had typical pernicious anemia, and six of these had been under observation and treatment with liver extract no 343, administered orally, over a period of time ranging from six months to four years. Previous reticulocyte responses in certain of these patients, with essentially little variation in the potency of the material throughout, afford useful information in comparing the effectiveness of liver extract no 343 when administered orally and when injected intravenously. The remaining three cases of anemia resembled hemolytic jaundice, however, the characteristics of the red blood cells and the other observations on the blood, except for the persistently high reticulocyte counts, could not be differentiated from those in pernicious anemia during relapse.

#### TECHNIC AND EFFECTS OF INJECTION

After a sufficient control period, the patients received, at a single injection, 20 cc of liver extract (the amount derived from 100 Gm of liver). The usual daily observations of the blood were made, and injections were given at regular weekly intervals, unless some definite contraindication arose.

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5 Strauss, M B, Taylor, F H L, and Castle, W B. Intramuscular Use of Liver Extract, *J A M A* **97** 313 (Aug 1) 1931.

6 Gansslen, M. Ein hochwirksamer, injizierbarer Leberextrakt, *Klin Wchnschr* **9** 2099 (Nov 8) 1930.

The liver extract was brought to body temperature before injection. During and immediately following each injection the patient was observed closely for the occurrence of a reaction, and the blood pressure was taken and recorded at intervals of one minute. The rate of injection ranged from 0.5 to 2 cc per minute, depending on the response of the patient.

There were a generalized flush to the skin and a sensation of excessive heat in all the patients during the time of the injection. Ninety-five injections were given, and chills were noted following five of these. Four of the chills followed the initial injection, and the fifth on a second injection. All of the chills were mild and lasted about fifteen minutes. The blood pressure decreased slightly at some time during the injection in essentially all patients, but rapidly returned to its original level. The average decrease in the systolic blood pressure during the ninety-five injections was 26 mm of mercury, and the average decrease in the diastolic blood pressure, 16 mm. At no time did the systolic blood pressure fall below 80. Slight increases in blood pressure were observed in a few instances during the process of injection. Three patients (cases 1, 5 and 7) always had slightly labored respirations during the injections, and in one instance precordial pain was noted when the blood pressure fell. Nausea, vomiting and abdominal cramps rarely occurred. The urine voided following the injections was usually dark amber in color, but no casts, red blood cells or increase in albumin were observed.

While none of the reactions was of a serious character, the slow administration of the substance is recommended.

#### REPORT OF CASES

CASE 1—This patient was a white woman, aged 50, married, who had hemolytic jaundice. She had a severe macrocytic anemia which could not be differentiated from that of pernicious anemia during relapse, except for a persistent reticulocytosis. Both the spleen and liver were markedly enlarged and firm. There were no evidences of neurologic involvement, the temperature fluctuated, with daily rises to 101 F, the blood bilirubin content was 1 mg per hundred cubic centimeters, and a definite icterus of the skin and sclerae was present. Free hydrochloric acid in the gastric contents was absent following the administration of histamine. A typical blood response and rapid clinical improvement followed the injection of liver extract intravenously.<sup>7</sup> The red blood cells reached a normal level after seven injections of liver extract, as is clearly shown in chart 1. A maximal reticulocyte response, reaching 624,000 per cubic millimeter of blood (47.5 per cent), was obtained in the presence of a fever, followed by a normal temperature. Secondary rises in the reticulocytes were observed four days after the second and third injections, respectively, even though the initial reticulocyte response appeared to be maximal.

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<sup>7</sup> Unless otherwise mentioned, each intravenous injection of 20 cc contained the amount of active principle derived from 100 Gm of liver.

CASE 2—A white woman, aged 31, with hemolytic jaundice entered the hospital with essentially the same clinical and laboratory picture as that recorded in case 1. She had been under observation for a year, when she first entered the hospital, one year before, she was in a state of relapse, jaundiced and critically ill. She was given both liver extract no. 343 and ventriculin by mouth, at separate periods, with an unsatisfactory reticulocyte response following both. On the continued administration of liver extract derived from 300 Gm of liver daily, the red blood

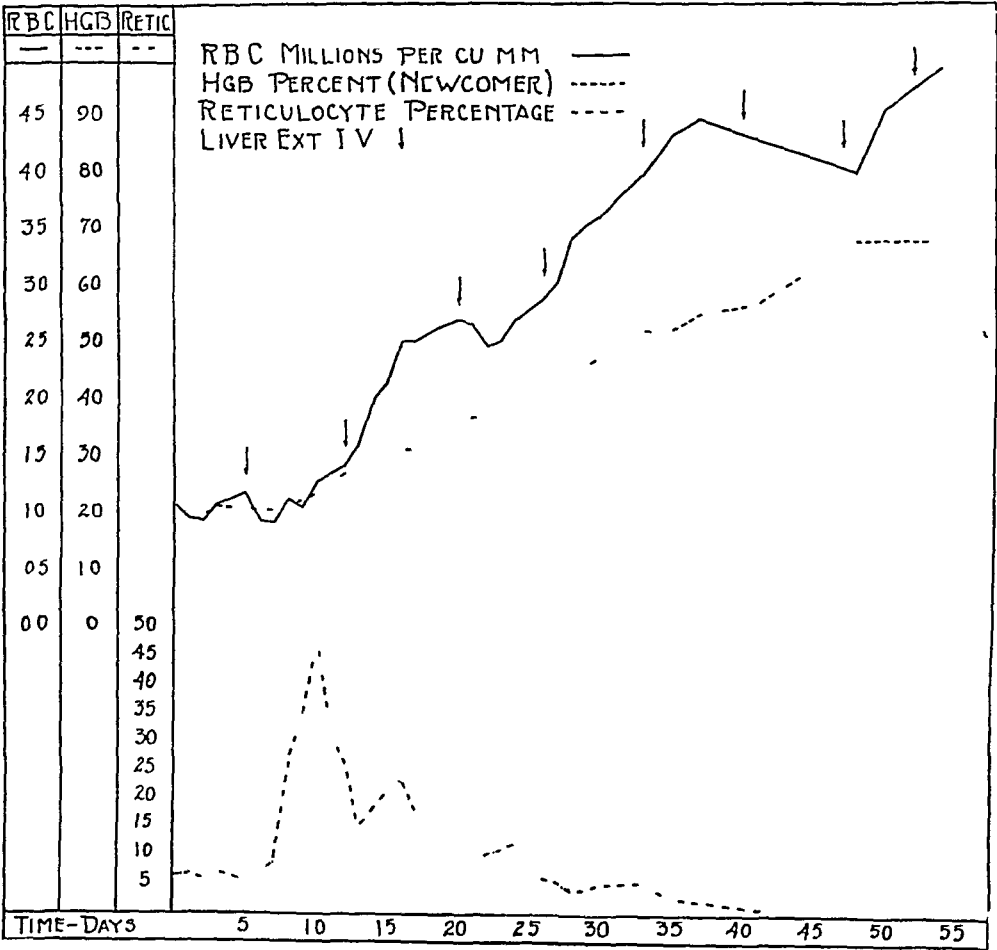


Chart 1—Response of the red blood cells, hemoglobin and reticulocytes in a patient (case 1) with hemolytic jaundice to liver extract given intravenously (Extract derived from 100 Gm of liver given at each injection)

cells eventually reached normal, remaining at a level of approximately 4,500,000 per cubic millimeter of blood until two months prior to the patient's present entry into the hospital

During the period of two months previous to her present admission, the red blood cells dropped from 4,500,000 to 1,600,000 per cubic millimeter of blood, despite the daily administration of liver extract derived from 400 Gm of liver. On admission, the patient was given two blood transfusions of 500 cc each, liver extract derived from 600 Gm of liver daily for thirty days, and 0.18 Gm of metallic iron (iron and ammonium citrate) daily for fourteen days, without a satisfactory response of the red blood cells. When liver extract derived from

75 Gm of liver was given intravenously, there was a very satisfactory response of the reticulocytes and a marked improvement occurred in the patient's clinical condition (chart 2)

Castle and Taylor<sup>1</sup> reported the case of a patient with pernicious anemia who failed to respond to the daily oral administration of liver extract derived from 300 Gm of liver over a period of ten days, but

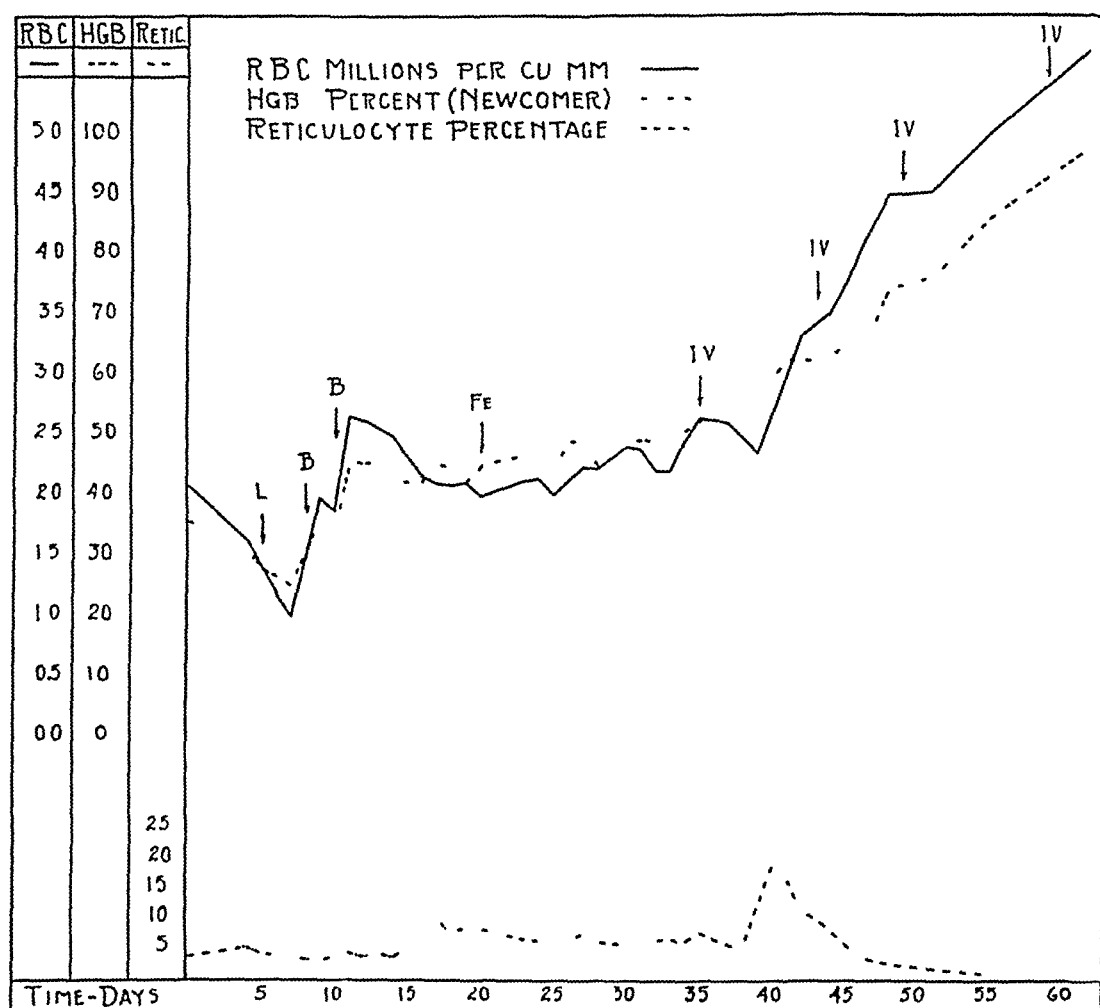


Chart 2—Response of red blood cells, hemoglobin and reticulocytes of a patient (case 2) with hemolytic jaundice to (L) liver extract no 343 derived from 600 Gm of liver daily, (B) a blood transfusion of 500 cc of whole blood, (Fe) 0.18 Gm of metallic iron (iron and ammonium citrate) daily, (IV) liver extract given intravenously in amounts of 15, 5, 20 and 8 cc, respectively (20 cc was derived from 100 Gm of whole liver)

who did respond to a single intravenous injection of liver extract derived from 100 Gm of liver

CASE 3—A white man, aged 54, with a typical case of pernicious anemia, had two distinct relapses that responded to liver extract no 343 and one relapse that responded to ventriculin, 30 Gm daily. The maximum reticulocyte response following the administration of ventriculin reached 47 per cent (absolute number

643,000 per cubic millimeter of blood) at an initial level of 1,340,000. The red blood cell count reached a normal level and remained there for six months. During the next seven months the red blood cell count remained below 4,000,000, even though the patient took the amount of liver extract derived from 300 Gm of liver daily during the entire thirteen months.

Liver extract derived from 100 Gm of liver was given intravenously at an initial level of 3,650,000 red blood cells per cubic millimeter, and a reticulocyte response of 5.6 per cent was obtained. After five intravenous injections, the red blood cell count reached 5,430,000 and the hemoglobin content 101.2 per cent.

CASE 4—This patient was a white woman, aged 59, married, who entered the hospital recently because of cardiac failure. She had a typical case of pernicious anemia and had been under observation since October, 1927. During this period she had had frequent relapses because of the voluntary omission of liver extract therapy. Seven definite reticulocyte responses were obtained, as recorded in the accompanying table. Except in one instance, the absolute number of reticulocytes resultant from one injection of liver extract was greater than any of the reticulocyte responses obtained when liver extract was given by mouth, even though

*The Height of the Reticulocyte Responses Following Varying Amounts of Liver Extract by Mouth and One Intravenous Injection of Liver Extract in the Same Patient (Case 4)*

Date Treatment Began	Liver Extract Derived from Gm Liver	Day of Reticulocyte Peak	Reticulocytes, per Cent	Red Blood Cells per C Mm	Hemoglobin (New comer), per Cent	Absolute Number of Reticulocytes, per C Mm at Peak
1/7/28	600 daily	6	25.9	1,270,000	29.4	328,000
10/8/28	300 daily	10	6.6	1,800,000	45.3	118,800
11/22/28	300 daily	8	14.3	2,250,000	49.6	321,000
1/4/30	300 daily	6	18.7	2,110,000	44.6	394,570
2/10/30	300 daily	5	13.8	1,820,000	44.6	251,160
8/11/30	300 daily	5	8.5	2,440,000	41.6	251,160
6/27/31	100 intravenously	4	11.2	3,250,000	65.5	364,000

the initial red blood cell level was above 3,000,000. Within three weeks after the initial injection of liver extract, the red blood cell count had reached 4,750,000 per cubic millimeter.

CASE 5—A white man, aged 48, married, who had typical pernicious anemia, entered the hospital while recovering from bronchopneumonia and during a severe relapse. Chart 3 shows the magnitude of the hematopoietic response to the first and subsequent injections of liver extract.

CASE 6—A white woman, aged 71, with typical pernicious anemia complicated by a severe chronic nephritis, first entered the hospital in August, 1927. A reticulocyte response of 49.4 per cent was obtained at an initial level of 840,000 red blood cells, when liver extract derived from 400 Gm of liver was given daily. Since that time the patient had taken liver extract derived from 200 to 300 Gm of liver daily. She entered the hospital recently because of gross hematuria and an acute exacerbation of a chronic nephritis. The blood nonprotein nitrogen was high, but after it returned to normal, the patient was given liver extract intravenously, when the red blood cells were at a level of 3,670,000 per cubic millimeter. The reticulocytes increased to 4.4 per cent, which was followed by a rise in the red blood cells to 4,300,000 within three weeks' time.

CASE 7—A white man, aged 55, with typical pernicious anemia, entered the hospital because of acute progressive neurologic changes, accompanied by a rather

severe diarrhea and a sore tongue. This patient had been under our observation for six months and had taken regularly the amount of liver extract derived from 300 Gm of liver daily. The red blood cell count during that time had been maintained at a level of approximately 4,500,000, but, on the patient's entrance to the hospital, it was found to have decreased to 3,970,000. Injections of liver extract were given for four consecutive weeks with no increase in reticulocytes or red blood cells, but the patient improved symptomatically. Subsequently, two injections weekly were given for a period of seven weeks, after which time the number was reduced to one per week. Although the response of the patient to

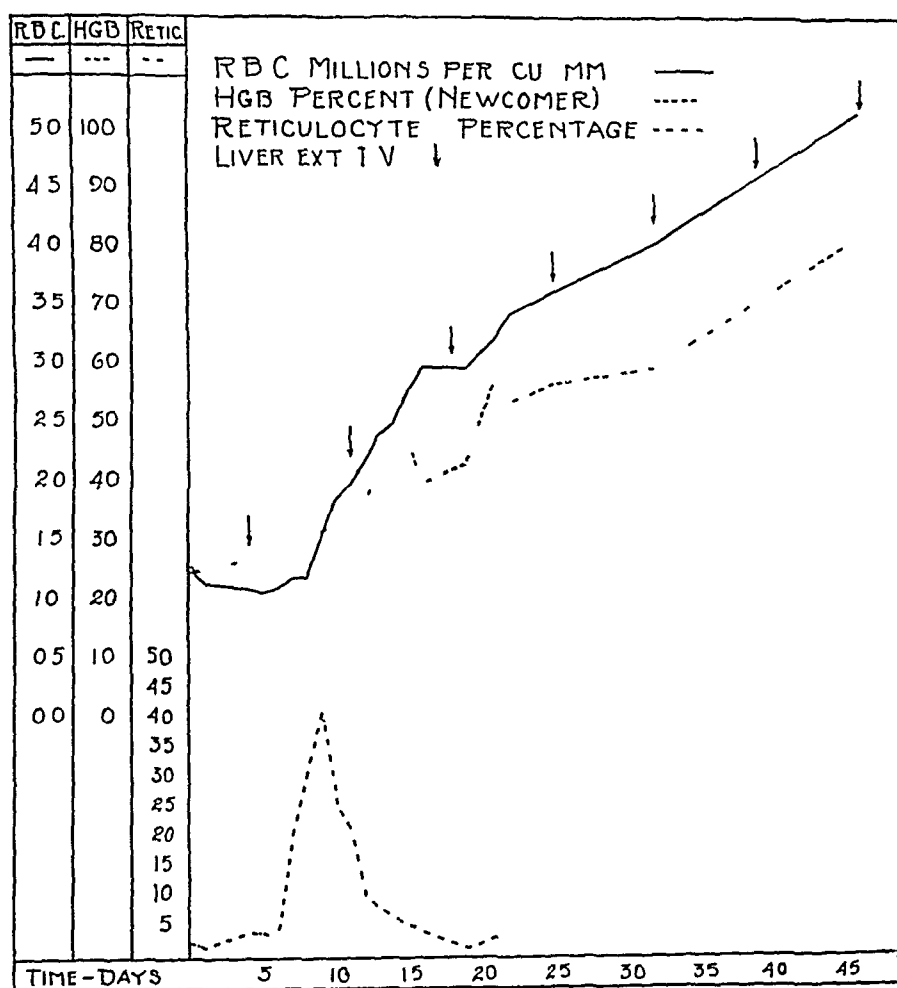


Chart 3—Effect on red blood cells, hemoglobin and reticulocytes when liver extract derived from 100 Gm of whole liver was given intravenously at weekly intervals to a patient (case 5) who had pernicious anemia

liver extract given intravenously was slow, requiring four months for the red blood cells to reach 5,000,000, the count has been maintained approximately at this level for four months.

CASE 8—This patient, a white woman, aged 55, with typical pernicious anemia and marked cord changes, entered the hospital during her third relapse. She had not taken liver extract or liver for two years until approximately three weeks prior to her entry to the hospital. During the three weeks, she took liver extract derived from 8,300 Gm of liver and, consequently, had improved clinically. The red blood cells numbered 2,720,000, the hemoglobin amounted to 57.3 per cent

and the reticulocytes to 0.8 per cent. Apparently the patient had had a reticulocyte response resulting from the liver extract ingested, and, as a result, there was only a slight increase in reticulocytes (4 per cent) following one injection of liver extract intravenously. After four injections of liver extract the red blood cells reached approximately a normal level.

CASE 9—A white woman, aged 55, with typical pernicious anemia, was first treated with liver extract during a relapse in April, 1929. The red blood cells at that time numbered 1,100,000, and the patient was given the amount of extract derived from 600 Gm of liver daily. The maximum reticulocyte peak reached was 28 per cent (487,200 was the absolute number of reticulocytes). After the red blood cells reached normal, the amount of extract derived from 300 Gm of liver was sufficient to maintain a red blood cell level of approximately 4,500,000, although the patient had had acute attacks of pyelitis frequently since November, 1929.

During the six months prior to her present admission to the hospital she failed to report for examination, the spinal cord signs and symptoms progressed, and the red blood cells decreased to a level of 2,190,000. Although she had a low grade fever, resulting from an acute exacerbation of a chronic cystitis and pyelitis, a reticulocyte response of 17.5 per cent (absolute number of reticulocytes, 382,700) was obtained on the fifth day, following one intravenous injection of liver extract. After three injections, the red blood cell count reached 4,150,000.

CASE 10—A white man, aged 27, entered the Methodist Hospital in June, 1929, complaining of loss of weight, diarrhea, weakness, palpitation and swelling of the ankles. On physical examination he was markedly jaundiced, emaciated and mentally depressed. The spleen was enlarged, and there was considerable edema of the ankles. There were no evidences of cord involvement. The red blood cell count was 1,280,000 per cubic millimeter, with hemoglobin 24 per cent and reticulocytes 0.8 per cent. The blood smears were not distinguishable from those of pernicious anemia during relapse. Free hydrochloric acid was present in the gastric contents.

The patient was given the amount of liver extract no. 343 derived from 300 Gm of liver daily. Unfortunately, no reticulocyte counts were made during the early course of his treatment, however, after four months' time, the red blood cell count reached 4,940,000, the hemoglobin content was 83.3 per cent, and there was a striking clinical improvement in the patient. Liver extract therapy was then voluntarily omitted, and, after two months' time, the signs and symptoms that were present on the patient's admission returned, and the red blood cell count decreased to 2,240,000 per cubic millimeter.

On resuming liver extract therapy, he improved clinically, and the red blood cell count reached 4,390,000 within three months' time. The red blood cell counts were maintained at essentially normal levels for a period of ten months, and during this time the patient continued to take the amount of extract derived from 300 to 400 Gm of liver daily. However, for no apparent reason, his red blood cells decreased to 2,400,000 during the ensuing two months. On admission to the outpatient department, he was given one injection of liver extract intravenously, and on the fifth day of treatment the reticulocyte count reached 13.2 per cent (absolute number of reticulocytes, 403,900). Within thirty-nine days, the red blood cell count was 5,090,000, and the hemoglobin 91.7 per cent. The injections of liver extract were then discontinued, and the patient received daily, by mouth, the amount of liver extract no. 343 derived from 300 Gm of whole liver. Within four months he had another relapse, the red blood cells reaching a level of

1,730,000 and the hemoglobin 37.3 per cent. Following one intravenous injection of liver extract the reticulocytes reached a peak of 26.6 per cent.

The diagnosis in this case is not clear, although the clinical features resemble those of hemolytic jaundice more than those of pernicious anemia.

#### COMMENT AND SUMMARY

The preparation of a solution of liver extract no. 343, after the method described by Castle and Taylor,<sup>8</sup> has been found to contain the active principle in liver effective in the treatment for pernicious anemia and suitable for intravenous administration.

The potency of a small amount of liver extract administered intravenously, as reported by Castle and Taylor, has been fully confirmed by our results in the treatment of seven patients with pernicious anemia and three patients with hemolytic jaundice. Cases 2, 3, 4, 9 and 10 also illustrate that small amounts of liver extract, given intravenously, have been effective in patients whose red blood cells were not maintained at normal levels, although the amount of potent extract derived from 300 to 600 Gm. of liver had been given daily, by mouth, over a period of time. This suggests, as Castle and Taylor pointed out in their paper, that there is possibly a defective absorption of the active principle from the gastro-intestinal tract in such cases. It would also seem, from our experience and from that of others, that there is a considerable variation in individual patients and in the same patient in this respect. While it is definitely known that most therapeutic agents are much more effective when given intravenously than when given by mouth, it would appear that, in the case of liver extract, the difference in potency cannot be accounted for entirely by this variation. In the presence of persistent diarrhea, nausea and vomiting and in the treatment of certain fastidious patients, the intravenous method of administration should also be of considerable value.

It is generally known<sup>8</sup> that, in the presence of infectious processes, fever and intoxication, liver extract given by mouth has been relatively ineffective. Cases 1 and 9 show that liver extract administered intravenously was highly efficacious in the presence of fever.

One of us treated three patients with pernicious anemia in whom, while sufficient amounts of liver extract were taken by mouth, acute progressive spinal cord changes developed, accompanied by a severe anemia that did not respond to very large daily amounts of liver extract.

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<sup>8</sup> Minot, G. R., and Murphy, W. P. A Diet Rich in Liver in the Treatment of Pernicious Anemia, *J. A. M. A.* **89**: 759 (Sept. 3) 1927. Minot, G. R., Murphy, W. P., and Stetson, R. P. The Response of the Reticulocytes to Liver Therapy, *Am. J. M. Sc.* **175**: 581 (May) 1928. Smithburn, K. C., and Zerfas, L. G. The Inhibitory Action of Infection and Fever on the Hematopoietic Response in a Case of Pernicious Anemia, *Ann. Int. Med.* **4**: 1108 (March) 1931.



It is probable that, under such circumstances, liver extract administered intravenously would have been of great value

In cases 3, 4 and 6, in which the initial red blood cell levels were 3,650,000, 3,250,000 and 3,670,000 per cubic millimeter, respectively, slight but distinct reticulocyte rises were obtained following the intravenous administration of extract derived from 100 Gm of liver. This is in contrast to the absence of reticulocyte responses reported by Minot,<sup>9</sup> one of us (Dr Zerfas<sup>10</sup>) and others when large amounts of potent fractions of liver were given daily by mouth to patients whose initial red blood cell counts were much above 3,000,000

Although the reticulocyte peak is reached sooner when liver extract is given intravenously than when it is given orally, we do not believe that its use alone will suffice in patients who are desperately ill. It would appear, however, that the intravenous use of liver extract supplementary to blood transfusions is indicated in this type of case.

Two cases of hemolytic jaundice (cases 1 and 2), with severe macrocytic anemia, showed maximal reticulocyte responses following one intravenous injection of liver extract, a third case (case 10), possibly one of hemolytic jaundice, responded in a similar manner.

While we believe that the intravenous administration of liver extract will not supplant its use by mouth, we are convinced that its supplementary use, intravenously, will be of distinct benefit in the therapy of pernicious anemia and possibly in other macrocytic anemias.

NOTE—Since submitting this paper for publication, twenty-five additional patients with primary pernicious anemia have been treated with liver extract administered both intramuscularly and intravenously, making a total of five hundred injections. In every instance the clinical improvement and the hematologic response have been as striking as in the ten cases here reported.

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9 Minot, G. R., Cohn, E. J., Murphy, W. P., and Lawson, H. A. Treatment of Pernicious Anemia with Liver Extract, *Am J M Sc* **175** 599 (May) 1928.

10 Zerfas, L. G. Liver Extract in Pernicious Anemia, *Arch Int Med* **47**. 135 (Jan) 1931.

# VARIATIONS IN THE TOTAL BLOOD LIPID IN ALIMENTARY LIPEMIA

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The present investigation was conducted in an attempt to determine whether in the absence of pancreatic or hepatic disease the concentration of the total blood lipid at fixed intervals after the ingestion of a large amount of fat adhered to a typical pattern. If a typical curve were demonstrated, a method similar to the dextrose tolerance test could then be employed to discover what modifications were produced by such disease. The total blood lipid was chosen as an indicator of lipolytic activity largely because it could be estimated by a relatively simple method requiring only small amounts of blood.

## METHOD

The procedure was as follows. After a twelve hour fast, a specimen of blood was withdrawn. The subject immediately thereafter drank 100 cc of olive oil. Samples of blood were then taken two, three, four, five and six hours after the ingestion of the oil. In many instances, the fifth hour determination was omitted, while in a small number a seventh hour specimen was added.

The total alcohol ether extract was determined by a method developed by Bernhard in the Achelis laboratory. A strip of fat-free filter paper (Whatman no 100, fat-free, for milk analysis) measuring about 160 mm was cut in half lengthwise. It was then impregnated with 1 cc of whole blood, spread out in such a manner that it occupied about seven eighths of the length of the paper. After air-drying for one-half hour, it was folded in a manner similar to a folded filter, and placed in a Folin sugar tube to which was added 4 cc of a mixture of equal parts of 95 per cent ethyl alcohol and pure ether. A condenser was placed in the Folin tube, and the mixture allowed to reflux for one hour on a slow boiling water bath. (During the extraction, care must be exercised that the alcohol ether mixture does not evaporate below 3 cc.) The condenser was then removed and the extract transferred to a weighed porcelain crucible. The Folin tube was washed four times with 5 cc portions of alcohol ether, and the washings were added to the crucible. The extract, with the added washings, was evaporated on the water bath and the crucible then placed in a desiccator for two hours and weighed on the Bunge microbalance. All determinations were made in duplicate. As I was interested in comparative curves, estimations of the various fractions of the total lipid were considered unnecessary in the present study. Many such estimations

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From the service of Dr Packard at the Gouverneur Hospital and the Achelis Laboratory of the Lenox Hill Hospital

were performed, however, during the course of the work, and the variations in the cholesterol and lipid phosphorus were found to be so slight that their effect on the curve could be disregarded

To establish normal figures with these technical procedures, the test was performed on sixty-seven patients grouped as follows group A, seventeen healthy men received through an employment agency, and group B, fifty patients (forty-six men and four women) afflicted with a variety of illnesses, patients with pancreatic (including diabetes mellitus) or liver disease being excluded as carefully as the present methods would permit. In those suffering from an acute infectious disease the examination was made after at least a week of convalescence, and in the cardiac group, after compensation was restored. During the test, those in group A were ambulatory, while the majority in group B were confined to bed.

TABLE 1—*Variation in the Total Blood Lipid in Seventeen Normal Men Following the Ingestion of Olive Oil*

Case	Patient	Sex	Age	Total Lipid, Mg per 100 Cc					
				Fasting	2 Hrs	3 Hrs	4 Hrs	5 Hrs	6 Hrs
1	N I	M	21	820	860	820	840	870	860
2	S T	M	22	720	620	620	870	880	880
3	R O	M	23	850	940	850	800	940	980
				860	950	870	820	920	980
4	W H	M	22	870	1,070	920	810	890	
5	L E	M	24	840	880	920	950	970	1,000
6	L I	M	25	840	880	950	1,060	1,020	970
7	I H	M	27	920	980	940	810	910	1,040
8	G A	M	28	840	830	860	800	900	860
9	S R	M	30	660	720	730	780	790	720
10	S M	M	30	840	830	830	780	820	880
11	S H	M	33	660	740	750	780	770	850
				660	720	740	720	700	880
12	S I	M	34	900		940	900	1,010	1,000
13	E L	M	35	830	940	1,000	1,090	1,050	920
				840	940	1,030	1,030	950	860
14	S W	M	35	840		930	610	550	840
15	D I	M	37	1,010		1,070	1,100	950	1,010
16	L U	M	40	1,120	1,100	1,030	1,000	1,000	1,030
17	H O	M	48	850	980	1,000	940	1,010	920
Maximum				1,120	1,100	1,070	1,100	1,050	1,040
Average				844	881	890	874	895	909
Minimum				660	620	620	610	550	720

After a lapse of several days or weeks, the test was repeated in five cases, in two, additional tests were performed to ascertain the effect of starvation and the ingestion of 100 Gm of dextrose on the blood lipid curve.

#### COMMENT

Analysis of the figures presented in tables 1 and 2 shows that, following the drinking of 100 cc of olive oil, the variations in the total blood lipid, instead of adhering to a single typical pattern, fall into three main types which I have arbitrarily termed the ascending, flat and descending. Considering a rise of 100 mg or more as significant, 63.2 per cent of the patients gave an ascending, 17.5 per cent a flat and 19.3 per cent a descending type of curve. It is interesting to note that Rohdenburg, Bernhard and Krehbiel<sup>1</sup> performed the dextrose tolerance

1 Rohdenburg, G. L., Bernhard, A., and Krehbiel, O. A Study of Sugar Mobilization Based upon 228 Human Cases, *Am J M Sc* **159** 577, 1920.

TABLE 2—*Variations in the Total Blood Lipid in Fifty Patients Following the Ingestion of Olive Oil*

Case	Patient	Sex	Age	Total Lipid, Mg per 100 Cc							Diagnosis
				Fasting	2 Hrs	3 Hrs	4 Hrs	5 Hrs	6 Hrs	7 Hrs	
1	W R	M	23	730	900	1,040	995	1,010	1,020		Influenza
2	M E	M	25	990	1,100	1,050	1,070	1,090	870		Lobar pneumonia
3	A C	M	25	930	910	920	930	950	980		Acute rheumatic fever
4	H Mc	M	26	1,040	1,000	1,060	1,110	1,110	1,040		Lobar pneumonia
5	P M	M	26	1,060	1,060	990	960		900		Influenza
6	H S	F	27	1,060	1,160	1,030	1,140		1,050		Acute rheumatic fever
7	S L	M	31	1,130	1,210	1,230	1,210	1,200	1,180		Lobar pneumonia, postencephalitic paralysis agitans
8	N M	M	32	1,040	1,100	1,120	1,210		1,310		Acute infectious arthritis
9	J O	M	34	1,200	1,370	1,100	1,090		1,100		Submersion, bronchopneumonia
10	J M	F	34	780	850	880	810	820	830		Chronic endocervicitis
11	O L	M	35	1,020	1,150	1,160	1,195		1,100		Gastric ulcer
12	M P	M	37	910	1,000	1,010	1,065		920		Acute arthritis
13	C L	M	37	940	890	850	855		770		Acute bronchitis
14	B O	M	37	1,090	1,190	1,460	1,460	1,480	1,200		Acute rheumatic fever
15	B C	M	38	1,010	1,110	1,120	1,010		920		Chronic valvular disease
16	A Z	M	40	990	1,010	1,130	1,170		1,120		Psychoneurosis
17	D C	M	40	950	1,100	1,025	1,220		980		Lobar pneumonia
18	J B	M	41	1,010	1,240	1,220	1,240		1,470		Influenza
19	L F	M	42	870	860	950	1,005	1,310	1,130	1,010	Carbon monoxide poisoning
20	J D	M	42	990	1,110	1,110	1,245		1,200		Sacro iliac arthritis
21	W T	M	43	750	800	805	1,020		1,000		Lobar pneumonia
22	P M	M	42	1,030	1,120	1,150	1,010		1,160		Alcoholism, submersion
23	H S	M	43	960	1,100	1,240	1,130		1,200		Lobar pneumonia
24	A M	M	48	740	760	820	1,010		1,190		Influenza
25	D P	M	49	810	823	1,450	1,035	1,060			Carbon monoxide poisoning
26	J N	M	50	850	860	940	1,150		1,000		Sciatica
27	J L	M	53	840	910	940	950	1,020	1,120		Dextrocardia, alcoholism, starvation
28	R W	M	53	860	790	1,080	1,030		1,040		Syphilis, Charcot knee
29	G S	M	54	1,120	1,150	1,260	1,125	1,280	1,490		Neurosis
30	J A	F	54	970	900	1,040	1,310		1,190		Influenza, chronic nephritis
31	P M	M	40	1,100	1,180	1,120	1,175		1,040		Chronic nephritis
32	G S	M	42	1,160	1,100	1,060	1,000	1,000	1,060		Gastric ulcer, unsolved pneumonia, marked arteriosclerosis
33	A B	M	44	1,065	1,080	970	1,000		1,110		Arteriosclerosis, hemiplegia
34	J Z	M	45	1,090	1,180	1,180	1,100		1,210		Arteriosclerotic nephritis, emphysema
35	W Z	M	46	990	1,000	930	820	950	1,020		Coronary sclerosis, auricular fibrillation
36	H G	M	48	1,260	1,350	1,280	1,120		1,540		Moderate arteriosclerosis, myocardial degeneration
37	H S	M	50	990	1,100	985	1,030	1,080	1,120		Moderate arteriosclerosis, influenza
38	J D	M	50	1,070	1,200	1,080	1,035		1,100		Arteriosclerosis chronic bronchitis and emphysema
39	H C	M	51	1,020	1,010	1,100	1,095		1,120		Chronic nephritis
40	S S	M	52	1,000	970	1,000	920		940		Arteriosclerotic nephritis
41	L Z	F	54	1,040	1,220	1,420	1,310		1,340		Chronic nephritis
42	A R	M	55	1,080	870	845	935	890	760	900	Arthritis deformans, moderate arteriosclerosis
43	F B	M	56	1,070		1,079	1,033	1,144	1,218	895	Marked arteriosclerosis, cerebral thrombosis coronary sclerosis
44	T K	M	59	1,580	1,490	1,255	1,170	1,080		960	Arteriosclerotic heart disease
45	A P	M	60	1,180	1,330	1,320	1,300		1,200		

TABLE 2—*Variations in the Total Blood Lipid in Fifty Patients Following the Ingestion of Olive Oil—Continued*

Case	Patient	Sex	Age	Total Lipid, Mg per 100 Cc							Diagnosis
				Fasting	2 Hrs	3 Hrs	4 Hrs	5 Hrs	6 Hrs	7 Hrs	
45	P C	M	60	1,210	1,030	1,260	1,200		1,240		Arteriosclerotic heart disease, hypertension
46	M R	M	61	980	1,080	1,110	1,095		1,100		Arteriosclerotic heart disease, hypertension
47	D G	M	62	1,150	1,000	1,290	1,100	1,160	1,220		Arteriosclerosis, hypertension
48	A L	M	62	1,120	1,120	1,180	1,110		1,220		Arteriosclerotic heart disease
49	E O	M	65	1,010	990		1,120		1,130		Angina pectoris
50	J F	M	68	1,060	1,040	1,020	870	910	960		Arteriosclerotic heart disease
Maximum				1,580	1,490	1,450	1,460		1,540		
Average				1,030	1,067	1,094	1,082		1,109		
Minimum				730	760	805	810		760		

test in a large series of cases, and found that the blood sugar curves could also be differentiated into the three varieties indicated

In the group exhibiting the ascending curve, the maximum increase, with but few exceptions, lay between the third and sixth hours and had a definite tendency to occur later rather than earlier in the curve. The largest increase above the fasting level was 640 mg, or 60 per cent. The rise in the total lipid was rarely progressive, as a marked dip in the curve was often present, usually at the fourth hour, sometimes at the third hour and occasionally as early as the second hour. In only a few instances had the total lipid fallen to or below the fasting level at the sixth hour.

The flat type of curve did not usually approximate a straight line, but showed variations of less than 100 mg either above or below the basal line.

The descending type of curve exhibited either a progressive fall in the total lipid with each determination or, after a steep decline, there was a terminal approach toward the fasting level. The greatest fall from the fasting level was 620 mg.

The fluctuations in the total lipid apparently had no relationship to the variation in the composition or in the conditions under which the test was performed in both groups. When the average total lipid for each determination in the test was plotted (chart 1), two parallel lines were formed. The only difference between them was that the level of the group B curve was 200 mg higher than that of group A. This difference can be attributed to the inclusion of cases of nephritis in the former, many of which showed an initial lipemia.

Pronounced changes in the curves developed, however, when the entire series was subdivided on the basis of age and on the presence of arteriosclerosis, and the average total lipid was now charted (chart 2). The persons below the age of 35 exhibited a flat curve, the maximum

increase of 60 mg at the second hour remaining almost stationary to the sixth. Those over 35 years of age showed an ascending curve, which mounted rapidly to the fourth hour and then more slowly to its peak at the sixth hour. The average rise was 167 mg. The patients with moderate or advanced arteriosclerosis were all above 35 years of age, but when they were separately considered, the marked progressive increase

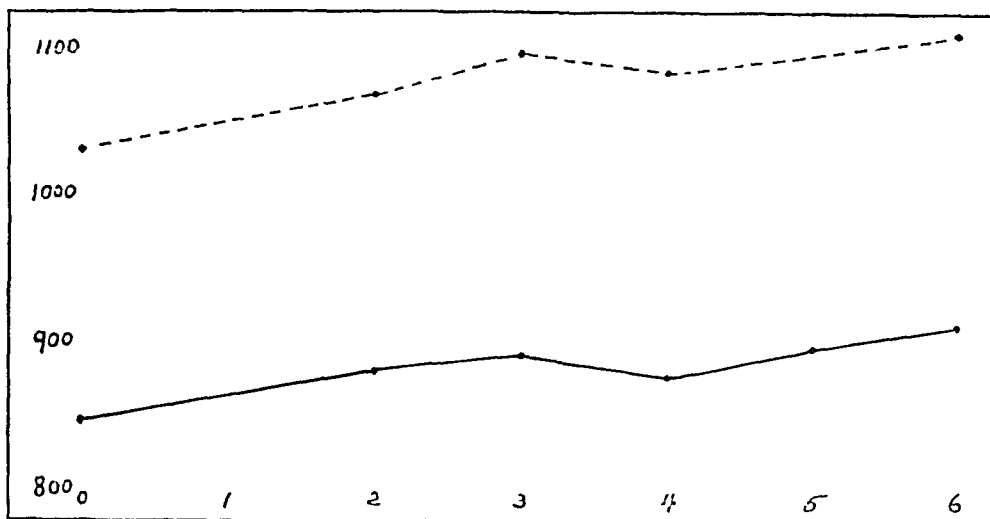


Chart 1—The average total blood lipid curves of groups A and B. The normal group (A) is represented by the solid line, the ward patients (B), by the dash line. The vertical scale indicates milligrams of total lipid per hundred cubic centimeters of blood, the horizontal scale, hours after the ingestion of olive oil.

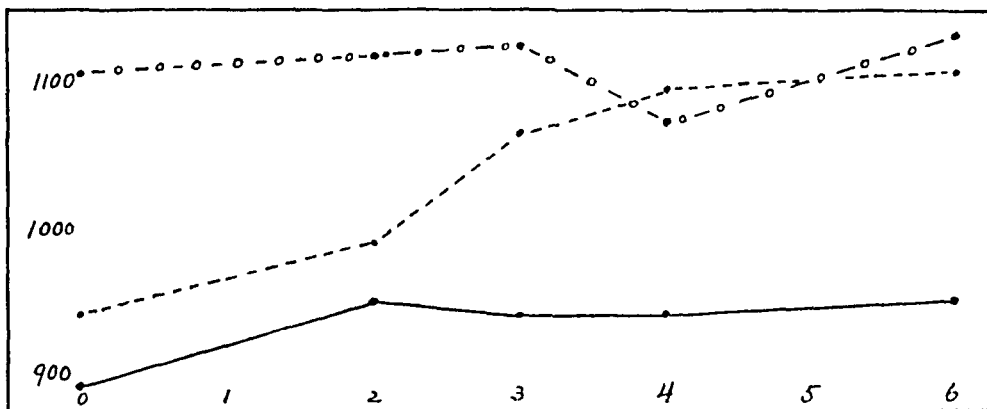


Chart 2—The average total blood lipid curves of persons below the age of 35 (solid line), of those above the age of 35 (dash line) and of those showing the presence of arteriosclerosis (circle line). The vertical scale indicates milligrams of total lipid per hundred cubic centimeters of blood, the horizontal scale, hours after the ingestion of olive oil.

in the total lipid was completely obliterated. Besides a pronounced drop at the fourth hour, the arteriosclerotic curve was even flatter than that of the younger group, as the maximum increase was but 26 mg. The average fasting level of the total lipid was only slightly influenced by

the age of the subject in contrast to its marked elevation by arteriosclerosis. Summarizing these observations in terms of the three types of curves. Subjects in the second and third decades usually exhibited a flat plateau, those in the fourth, fifth and sixth decades an ascending curve, and those showing evidence of arteriosclerosis a flat or descending curve with a higher fasting level.

Starvation produced a moderate progressive increase in the total blood lipid, the average rise being 75 mg. The substitution of 100 Gm of dextrose for the olive oil eliminated this starvation effect, and the resultant curve was practically a straight line (tables 3 and 4, chart 3).

Not only is the number of observations on the effect of fat feeding on the blood fat in both normal and pathologic states meager but the kind and amount of fat used and the technic of the blood analyses reported differ so widely that it is difficult to compare them with those in this study.

As early as 1907 Neumann<sup>2</sup> found that ultramicroscopic particles were to be seen in the blood two hours after a meal containing fat and

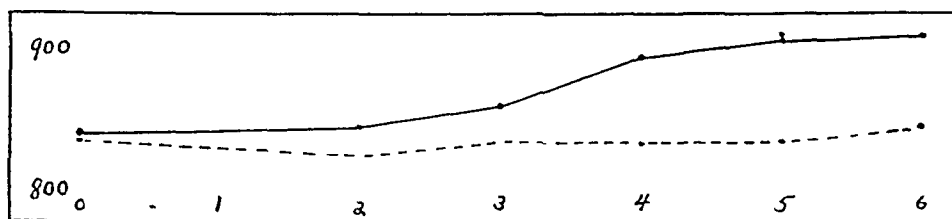


Chart 3—The average total blood lipid curves in starvation (solid line) and after the ingestion of 100 Gm of dextrose (dash line). The vertical scale indicates milligrams of lipid per hundred cubic centimeters of blood, the horizontal scale, hours.

that these were not present in the fasting state or after a fat-free meal. Recently, Strauss<sup>3</sup> examined the blood with the dark field for these particles from two to two and a half hours after a meal of 20 Gm of butter. He reported either no increase or a lowered blood fat in many patients suffering from senility, chronic alcoholism, chronic nephritis, chronic cardiorenal disease and cirrhosis of the liver.

In the same year, Neisser and Brauning<sup>4</sup> found that human serum was almost milky from three to five hours after the ingestion of 100 Gm of fat. Its turbidity was most marked six hours after the meal, and

2 Neumann, A. Ueber die Beobachtung des resorbierten Fettes im Blute mittels des Ultra-Condensers, *Zentralbl f Physiol* **21** 102, 1907.

3 Strauss, H. Prüfung der Fettresorption durch Erzeugung von alimentärer Lipämie, *Klin Wchnschr* **8** 2047, 1929.

4 Neisser, E., and Brauning, H. Verdauungslipämie, *Ztschr f exper Path u Therap* **4** 747, 1907.

it returned to normal six hours later. Burger and Habs<sup>5</sup> employed this observation, but modified the meal by adding 5 Gm of cholesterol to 100 cc of olive oil. They reported a pronounced turbidity of the serum four hours after the meal in all their cases except those of cirrhosis of the liver. Elmer and Scheps,<sup>6</sup> using the same technic, found the test to be wholly unreliable, as in two thirds of their normal cases the serum was either clear or only slightly turbid. Wendt<sup>7</sup> reported the same test negative in other conditions besides cirrhosis of the liver, such as abdominal carcinosis, tuberculous peritonitis, thrombosis of the portal vein, pericardial effusion and amyloidosis. Hirsch<sup>8</sup> added to this list complete occlusion of the common bile duct and a general depression of reabsorption, as in fevers and cachexia.

TABLE 3—*Variation in the Total Blood Lipid in Starvation*

Case	Patient	Sex	Age	Total Lipid, Mg per 100 Cc					
				Fasting	2 Hrs	3 Hrs	4 Hrs	5 Hrs	6 Hrs
1	R O	M	23	880	890	890	900	920	940
2	S H	M	33	800	800	830	890	890	890

TABLE 4—*Variation in the Total Blood Lipid Following the Ingestion of Dextrose*

Case	Patient	Sex	Age	Total Lipid, Mg per 100 Cc					
				Fasting	1 Hr	2 Hrs	3 Hrs	4 Hrs	5 Hrs
1	R O	M	23	860	840	840	840	860	880
2	S H	M	33	810	810	830	830	810	810

Bloor's nephelometric methods for blood fat have been made use of by several investigators. Cowie and Hoag<sup>9</sup> determined the total lipid content after a meal of analyzed cream in eight normal subjects, five children and three adults. They found it to be increased in all, with its maximum between the fifth and seventh hours in the former and at the sixth hour in the latter. They did not state either the amount or the percentage of increase. Starvation for four days in a boy aged 7 years caused the total lipid to increase 182 per cent, and in another subject,

5 Burger, M., and Habs, H. Ueber Störungen der Cholesterin und Fettresorption bei Lebercirrhose, *Klin Wchnschr* 6 2125, 1927, Die alimentare hypercholesterinämie beim stoffwechselgesunden Menschen, *Ztschr f d ges exper Med* 56 640, 1927.

6 Elmer, A. W., and Scheps, M. Die Cholesterin-Fettprobe bei Lebercirrhose, *Klin Wchnschr* 7 1083, 1928.

7 Wendt, H. Ueber Störungen der Fettresorption bei Lebercirrhose und anderen Erkrankungen, *Klin Wchnschr* 8 1566, 1929.

8 Hirsch, A. Ueber alimentäre Lipämie, *Klin Wchnschr* 9 2062, 1930.

9 Cowie, D. M., and Hoag, L. A. Studies in Blood Fat, *J A M A* 77 1493 (Nov 5) 1921.



64 per cent Van Slyke and his co-workers<sup>10</sup> fed 1 Gm of butter per kilogram to six normal subjects and seven patients with nephritis. Of the former, one showed an increase of 80 per cent, four an increase ranging from 13 to 29 per cent and one a decrease in the fatty acids of the plasma. Five nephritic patients with an initial lipemia exhibited increases of from 14.5 to 72.4 per cent, with an average of 45 per cent. Of the two subjects with a normal fasting level, the fatty acids remained stationary in one and rose but 4.5 per cent in the other. In the four experiments, on normal as well as on abnormal subjects, in which there was no increase of fat in the plasma, the rise in the metabolic rate and the fall in the respiratory quotient seemed to indicate that, nevertheless, fat was being effectively conveyed to the tissues. McClure and Huntsinger<sup>11</sup> reported an increase in the total fatty acids in fifteen normal subjects after a variety of food-stuffs such as oleic acid, olive oil (50 cc), dextrose, egg-white and a fat-free meal. This occurred between the third and the fifth hour except with the fat-free meal, when it was present at the third hour. The rise was most pronounced with oleic acid and olive oil. Starvation caused a rise of 12 per cent in one case, but in the others the changes were negligible. Page, Pasternack and Burt,<sup>12</sup> using 100 cc of olive oil as the meal, found the total lipid increased in seven of eight normal subjects.

Bang,<sup>13</sup> with his own method for estimating the fatty acids of the blood and a mixed meal containing 150 Gm of fat in the form of butter and cream, reported that most of his cases showed a slight rise, several no increase and one a decrease.

Even a cursory review of the literature indicates that a typical curve has not been obtained with any of the methods employed, and that the cause of these divergent results must be sought in the many uncontrolled factors present in such investigations, including the present one. Fluctuations in the blood fat can be explained in three ways: by variations in the rate of absorption of the ingested fat, in the mobilization of fat from the depots and in the rate of elimination of fat from the blood stream.

The rate of absorption is dependent on a large number of conditions: the emptying time of the stomach, the quantity and quality of the bile, the potency of the steapsin secreted by the pancreas and the state of the intestinal mucosa. Undoubtedly variations in these factors are present

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10 Heller, A., Linder, G. C., Lundsgaard, C., and Van Slyke, D. D. Fat Metabolism in Nephritis, *J. Exper. Med.* **39** 931, 1924.

11 McClure, C. W., and Huntsinger, M. E. Studies in Fat Metabolism *J. Biol. Chem.* **76** 1, 1928.

12 Page, I. H., Pasternack, L., and Burt, M. L. Ueber den Transport von Fetten und Lipoiden durch Blut nach Oleingabe, *Biochem. Ztschr.* **223** 445, 1930.

13 Bang, I. Ueber Lipämie, *Biochem. Ztschr.* **91** 104, 1918.

in apparently normal persons. However, such differences, even to the point of complete lack of absorption, could not explain a decrease in the blood fat. In addition, in the present experiments and in several of the reported cases, starvation produced a rise in the blood lipid.

It is well known that the large stores of fat that the body contains can be put at the disposal of tissues in need of a source of energy. Whether mobilization of the reserve fat occurs in human beings during fat digestion and absorption is still unproved. The discrepancy in the iodine number of the increased blood fat after the drinking of olive oil from that theoretically expected, as observed by McClure and Huntsinger<sup>11</sup> indicates that such mobilization may take place. Such a phenomenon however could only elevate the blood fat.

On the basis of a single variant, only differences in the rate of elimination could explain the three types of curve obtained in this study and by other investigators. Whether the rate of elimination actually varies is unknown. However, it is highly probable that all three factors play a rôle, comparable to the sugar regulatory mechanism, and that the blood fat at any particular time is the resultant of the interplay of these forces. How the age of the subject or the presence of arteriosclerosis modifies these factors is not elucidated by these experiments.

#### SUMMARY

1 The total blood lipid curves after the ingestion of 100 cc. of olive oil in sixty-seven subjects who were apparently free from pancreatic or hepatic disease are presented.

2 The curves could be subdivided into three categories: ascending, 63.2 per cent, flat, 17.5 per cent, and descending, 19.3 per cent.

3 The age of the subject and the presence of arteriosclerosis markedly influenced the total blood lipid. Persons in the second and third decades presented a flat curve, those in the fourth, fifth and sixth decades an ascending curve and those showing evidence of arteriosclerosis a flat or descending curve.

4 Starvation produced a moderate progressive rise in the total blood lipid.

5 Dextrose eliminated the starvation effect.

# INFLUENCE ON CARBOHYDRATE METABOLISM OF EXPERIMENTALLY INDUCED HEPATIC CHANGES

## I FASTING AND ADMINISTRATION OF THYROXINE

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This experimental study was undertaken in an attempt to gain more information on certain disturbances of carbohydrate metabolism previously noted in patients with diseases of the liver <sup>1</sup> The outstanding abnormality was an insufficiency of the blood sugar-regulating mechanism of the liver revealed by a modification of the dextrose tolerance test Following the injection of 20 units of insulin and the oral administration of 50 Gm of dextrose in 1,500 cc of water, normal persons were found to have a blood sugar curve that differed little from that obtained after the administration of 50 Gm of dextrose alone On the other hand, patients with hepatic disease after this test usually showed an initial rise of the blood sugar, which often exceeded the normal, and which was followed by an abrupt decline In some cases there was no initial rise, but an uninterrupted diminution of the blood sugar level Both types of curves ended in marked hypoglycemia

The questions involved in this series of experiments were (a) Can a low glycogen content of the liver, so often present in diseases of this organ, be responsible for deficient regulation of blood sugar? (b) Can one or both types of abnormal curves be reproduced in animals under similar conditions following the administration of the so-called specific hepatic poisons—phosphorus and chloroform? The effects of these poisons on carbohydrate metabolism are discussed in papers II and III of this series

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1 Althausen, T L, Gunther, L, Lagen, J B, and Kerr, W J Modification of the Dextrose Tolerance Test as an Index of Metabolic Activity of the Liver, Arch Int Med 46 1 (Sept) 1930

The important part played by the glycogen content of the liver in the functional activity of this organ and the diminution of this substance in the livers of many patients with hepatic disorders served as an inducement to investigate the possibility that a reduced amount of hepatic glycogen *per se* might be responsible for hypoglycemia following the modified dextrose tolerance test

The view that the glycogen is not a storage form of sugar but that it represents a balance between the processes of glycogenesis and glycogenolysis, which in turn are dependent on other phases of utilization of carbohydrates in the body, at present compels its acceptance by weight of experimental evidence. However, this does not preclude the possibility that a low glycogen content of the liver may be connected with abnormalities of sugar metabolism. This concept merely shifts the ultimate responsibility to conditions causing the reduction of hepatic glycogen.

Starvation was employed as one method of reducing the glycogen of the liver. For a check on the obtained results, thyroxine was employed in another series of animals.

#### METHODS

Young growing rabbits, nearly of the same age and weighing between 1,750 and 2,000 Gm, were selected as the most suitable animals for our purpose. Of these a few grew during the experiments to weigh between 2,000 and 2,200 Gm. Previous to any experiments, the rabbits were kept for at least two weeks on a constant diet of oats, which yield about 60 per cent anions and 40 per cent kations in the ash, and of green vegetables, in the ash of which the proportion of the respective ions is reversed. This was considered important, since Abderhalden and Wertheimer<sup>2</sup> demonstrated that changes of the acid-base balance induced in rabbits by diet affect the potency of insulin and epinephrine in these animals.

It was found that the combination of 5 Gm of dextrose in 100 cc of water administered by stomach tube immediately followed by a subcutaneous injection of 1 unit of insulin produced in rabbits a blood sugar curve similar to that of normal persons after the modified dextrose tolerance test. The usual previous overnight fasting was omitted in these animals because the morning blood sugar is lowered by this procedure and because considerable hypoglycemia had been observed between two and three hours after the test in fasting animals. In addition, very little would have been gained by it, since food is normally still found in the digestive tract of rabbits after five days of fasting.

The amount of dextrose chosen for the tolerance test was as small as possible in order to prevent distortion of the blood sugar curves due to glycosuria. The dosage of insulin (0.5 units per kilogram of body weight) and the amount of water were also kept as low as was consistent with a definite physiologic action in order to avoid overwhelming effects and to approach the relative amounts used for patients.

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<sup>2</sup> Abderhalden, E, and Wertheimer, E. Studien über den Einfluss der Ernährung auf die Wirkung bestimmter Inkrekstoffe. III. Insulin- und Adrenalinwirkung bei Verabreichung "saurer" beziehungsweise "basischer" Nahrung, Arch f d ges Physiol **205** 559, 1929.

In every experiment a specimen of blood sugar was taken from an ear vein before the test. After the administration of dextrose, water and insulin, two samples of blood were obtained at intervals of thirty minutes and two more at intervals of one hour. At the end of three hours the rabbits usually were given subcutaneous injections of 0.1 mg of epinephrine, and the blood sugar level was followed for two more hours at thirty minute intervals. In the use of this dose of epinephrine the object was to produce a rise in blood sugar that would begin to decline within the period of observation.

Determinations of the blood sugar were made each time in duplicate, according to the method described by Hagedorn and Jensen<sup>3</sup>

For glycogen analysis of the liver, rabbits were killed by decapitation or by a blow below the occiput. From 10 to 20 Gm of hepatic tissue, amounting to from

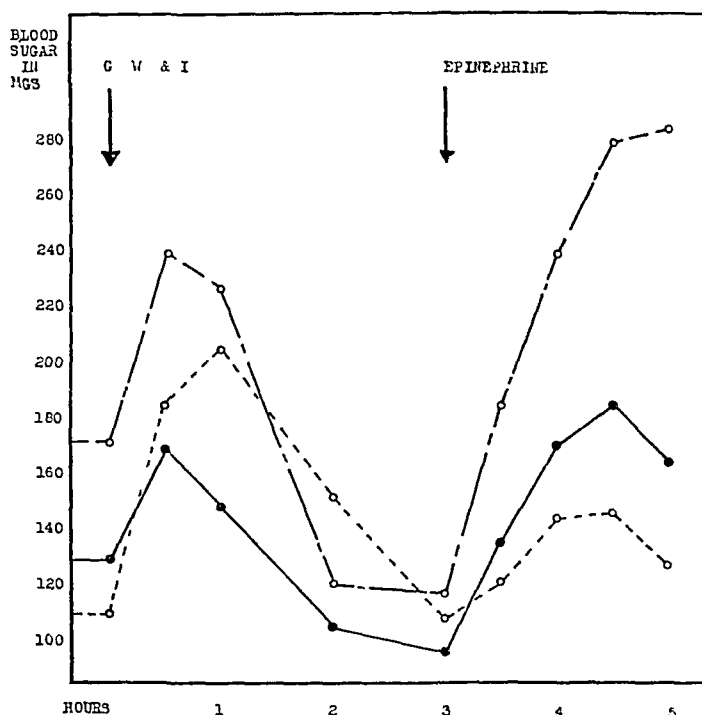


Chart 1—Blood sugar curves after the modified dextrose tolerance test and the administration of epinephrine in normal rabbits, fasting rabbits and those treated with thyroxine. The solid line represents an average of thirty-seven tests on normal rabbits. The regularly broken line shows the average of four tests on fasting rabbits. The irregularly broken line traces the curve of rabbit 751, which received the largest amount of thyroxine.

30 to 50 per cent of the total weight of the liver, was ground in ice-cooled alcohol and used for determinations of the glycogen by the Pfluger-Bertrand method. The glycogen determinations were made by Dr. Thoenes.

For histologic examination of the liver, two deep wedge-shaped pieces of tissue were removed from different parts of this organ and fixed in a diluted solution of formaldehyde, U. S. P. (1:10). From one part of the specimen, 5 micron paraffin sections were stained with hematoxylin and eosin. Frozen sections from the other part were stained with sudan III.

<sup>3</sup> Hagedorn, H. C., and Jensen, N. Zur Mikrobestimmung des Blutzuckers mittels Ferricyanid, *Biochem. Ztschr.* **135**: 46, 1923, *ibid.* **137**: 92, 1923.

TABLE 1—Blood Sugar Curves After the Modified Dextrose Tolerance Test and the Administration of Epinephrine in Normal Rabbits

Number	Weight, Gm	Blood Sugar After 5 Gm. of Dextrose in 100 Cc. of Water and 1 Unit of Insulin						Blood Sugar After 0.1 Mg. of Epinephrine					Average Blood Sugar for 3 Hr After Dextrose, 3 Hr. and Water and Insulin	Difference Between Average Blood Sugar for 2 Hr After Epine phrine and 3 Hr Blood Sugar
		Initial Sugar	1/2 Hr	1 Hr	2 Hr	3 Hr	Blood Sugar After 0.1 Mg. of Epinephrine							
							3 1/2 Hr	4 Hr	4 1/2 Hr	5 Hr	Difference Between Average Blood Sugar for 3 Hr After Dextrose, 3 Hr. and Water and Insulin			
												Average Blood Sugar for 2 Hr After Epine phrine		
717a*	2,030	112	155	162	119	83	112	151	194	166	129		+17	145
717b*	2,030	111	140	144	119	94	151	205	209	230	124	+13	182	+88
718	2,170	126	202	176	148	115	216	205	256	248	157	+31	215	+100
734a	1,800	124	130	140	104	83	158	151	144	140	116	+8	141	+58
734b	1,800	151	205	169	83	90	115	162	187	162	124	+14	148	+58
735a	1,950	140	184	166	112	133	122	148	140	162	147	+8	140	+7
735b	1,950	137	176	151	137	144					148	+11		
738	1,950	151	181	126	133	115	151	151	194	144	138	-13	157	+42
739	1,750	126	155	122	112	115	166	144	144	137	123	-3	145	+30
740a	1,750	126	202	187	112	90	119	187	187	155	158	+32	154	+64
740b	1,750	130	155	119	83	104	133	184	151	133	112	-18	144	+40
741	1,900	162	191	169	126	119	140	216	205	158	150	-12	178	+59
749	2,170	137	209	158	90	94	119	209	209	184	132	-5	164	+70
751	2,040	122	140	101	86	101	115	187	227	187	104	-18	224	+123
760	2,130	115	148	108	86	94	140	220	225	209	106	-9	193	+99
801a	1,850	133	169	162	148	151	173	144	158	148	154	+21	148	+12
801b*	1,850	151	176	156	148	137	140	166	166	151	153	+2	163	+11
803	1,770	133	155	126	108	119	140	158	151	151	124	-9	146	+27
804	1,770	158	162	104	104	72	119	151	158	144	126	-32	135	+63
811a	1,800	169	205	176	93	72	101	131	152	131	135	-34	121	+49
811b	1,800	141	227	184	126	61					148	+7		
814	1,700	108	130	137	108	65				133	112	+4		
816†	1,860	119	133	126	90	77	119	119			110	-9		
818	1,950	122	155	148	122	79					127	+5		
821	2,000	97	151	119	76	79					102	+5		
823	1,850	130	166	140	94	94					121	-9		
824	1,850	151	187	158	115	104					139	-12		
826	1,750	126	144	133	97	83					114	-12		
828†	1,850	144	176	173	108	115	112	126	122	115	140	-4		
829	1,760	137	212	202	108	119					153	+16		
830	2,160	151	194	173	137	130					156	+5		
831	1,870	115	169	137	83	90					115	0		
832	2,020	158	180	168	108	90					137	-20		
833	1,920	122	162	122	58	79					101	-21		
834	1,950	144	169	144	101	108					128	-16		
835	1,750	108	155	155	104	58					118	+10		
836	1,720	112	133	94	83	97					99	-13		
Average		132	170	150	107	99	137	173	186	167	129	-3	157	+53

## RESULTS

*Normal Rabbits*—Blood sugar curves three hours following the administration of dextrose, water and insulin were made on thirty-seven occasions for thirty-one normal rabbits. The individual data are given in table 1, and the average curve is plotted in chart 1. From the presented data it is seen that a normal curve, under the conditions of the test, has a characteristic shape and, within limits, a certain height.

As a basis of quantitative comparison with abnormal curves, the average blood sugar during the three hours of the test and the algebraic difference between the initial blood sugar and this average were found very useful. The peak of the curves usually paralleled the average blood sugar, but on the whole was less reliable. In two rabbits (816 and 828)

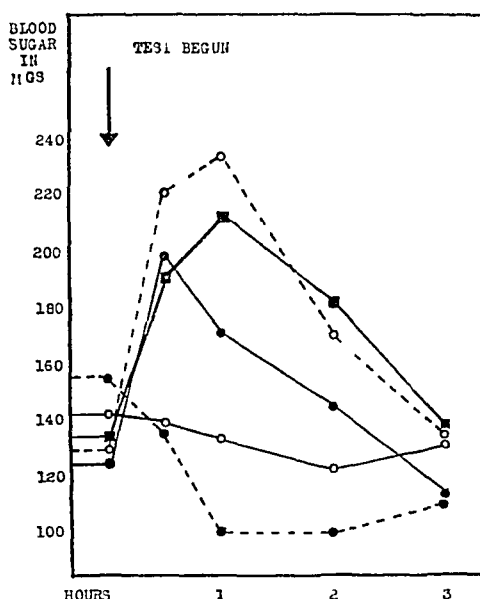


Chart 2—Blood sugar curves of a normal rabbit (718) after the administration of various combinations of dextrose, water and insulin. The solid line with disks shows the curve after the administration of dextrose, water and insulin, the solid line with squares, that after dextrose and water, the broken line with circles, after dextrose alone, the solid line with circles, after water only, and the broken line with disks after insulin alone.

that were followed for five hours after the test there was a gradual rise of the curve following a minimum at two hours.

In order to appraise the significance of the various factors involved in the production of the "normal" three hour curve, a series of experiments was carried out in which dextrose, water and insulin were given to the same rabbit singly and in various combinations, followed by the usual observations on the blood sugar. The results are given in table 2 and chart 2. Data on normal epinephrine curves are shown in table 1 and chart 1. From this the peak of the hyperglycemia due to epi-

TABLE 2—*Blood Sugar Curves After the Administration of Various Combinations of Dextrose, Water and Insulin in Two Normal Rabbits*

No	Test	Blood Sugar After 5 Gm of Dextrose in 100 Cc of Water and 1 Unit of Insulin					Blood Sugar After 0.1 Mg of Epinephrine				Average Difference Between Blood Sugar for 3 Hr After Dextrose, 3 Hr and Water and Initial Insulin Blood Sugar		Average Difference Between Blood Sugar for 2 Hr After Epine phrine and 3 Hr Blood Sugar	
		Initial Blood Sugar												
		1/2 Hr	1 Hr	2 Hr	3 Hr		3 1/2 Hr	4 Hr	4 1/2 Hr	5 Hr				
713	Dextrose, water and insulin	126	176	148	115		216	205	256	248	157	+31	215	+100
718	Dextrose and water	137	216	187	140		184	234	230	209	183	+46	232	+ 92
718	Dextrose	133	238	173	137						189	+56		
718	Dextrose	176	235	259	155						232	+56		
718	Water	144	140	126	137		205	223	263		134	-10	209	+ 72
718	Insulin	158	101	101	115		173	223	205	162	115	-43	185	+ 70
826	Dextrose, water and insulin	126	133	97	83						114	-12		
826	Dextrose	152	173	144	144						163	+11		

TABLE 3—*Glycogen Content of the Liver Before and After the Modified Dextrose Tolerance Test*

Normal Rabbits				Fasting Rabbits				Thyroxine Treated Rabbits			
Before Dextrose, Water and Insulin		After Dextrose, Water and Insulin		Before Dextrose, Water and Insulin		After Dextrose, Water and Insulin		Before Dextrose, Water and Insulin		After Dextrose, Water and Insulin	
Number	Glycogen, per Cent	Number	Glycogen, per Cent	Number	Glycogen, per Cent	Number	Glycogen, per Cent	Number	Glycogen, per Cent	Number	Glycogen, per Cent
23	5.70	807	10.8	20	0.7	810	2.25	742	0.6	802	2.20
176	4.50	808	9.6	775	1.0	812	1.55	840	0.7	809	3.04
744	7.85	814	5.2	806	0.6	822	2.17				
827	5.20					838	3.36				
Animals 4	Average % 5.81	Animals 3	Average % 8.5	Animals 3	Average % 0.76	Animals 4	Average % 2.33	Animals 2	Average % 0.65	Animals 2	Average % 2.62



nephrine can be expected to be reached between one and one and a half hours after the injection

The maximum rise in blood sugar after the administration of epinephrine and especially the average blood sugar for two hours following the injection, as well as the algebraic difference between these values and the blood sugar level before the injection, were of much greater assistance in detecting abnormal responses to epinephrine than the shape of the curve

Data on the amount of glycogen found in the liver of normal rabbits before and after the modified dextrose tolerance test are given in table 3. From these results it appears that the average glycogen content of the liver was increased by the administration of dextrose, water and insulin from 5.8 Gm per hundred grams to 8.5. Since these determinations of necessity were made for different animals, and since the higher figure is still within the limits of normal, the possibility must be considered that the increase is only apparent. On the other hand, taking into account the individual data that make up the average figure and the uniformity of the animal material kept on a constant diet, such a possibility does not seem probable.

*Fasting Animals*—Rabbits were prepared for the starvation experiment by withdrawal of all food for three days prior to the sugar tolerance and epinephrine tests. Data on the blood sugar curves of four animals subjected to such a fast will be found in table 4. The average curve is plotted in chart 1.

A comparison of blood sugar data obtained after fasting with those of the same animals in the normal state or with the average figures of all normal rabbits reveals several significant abnormalities. In analyzing the shape of the curves it is seen that in fasting rabbits the initial blood sugar is considerably lower. The peaks of the curves are higher than normal and are characteristically placed at the one hour period instead of the half hour period. The two hour blood sugar, which is normally lower than the initial blood sugar, is higher in all four fasting animals. Finally, in three cases even the three hour blood sugar is higher than the initial one. The exception in one case (734) in which the peak reached an unusual height of 230 mg is probably explained by spilling of sugar into the urine.

Figures for the average blood sugar before fasting, namely, 140 mg with an increase of 3 mg for the three hours, and after fasting, 163 mg with an increase of 51 mg, justify the impression already gained from the shape of the curves that the sugar tolerance of rabbits in this experiment was reduced.

The response to the administration of epinephrine was tested in three fasting animals, and was found markedly reduced in two cases and

TABLE 4—Blood Sugar Curves After the Modified Dextrose Tolerance Test and the Administration of Epinephrine in Fasting Rabbits

Number	Blood Sugar After 5 Gm. of Dextrose in 100 Cc. of Water and 1 Unit of Insulin					Blood Sugar After 0.1 Mg. of Epinephrine					Average Blood Sugar for 3 Hr.	Difference Between Average Blood Sugar and Average Blood Sugar for 2 Hr.	Average Blood Sugar for 2 Hr.	Difference Between Average Blood Sugar and Average Blood Sugar for 2 Hr.	
	Initial Blood Sugar	½ Hr	1 Hr	2 Hr	3 Hr					Dextrose, 3 Hr and Water and Initial Insulin Blood Sugar phrine Blood Sugar	+24	151	+65		
						¾ Hr	4 Hr	4½ Hr	5 Hr						
734	137	191	230	137	86	144	180	173	130	161					
735	104	198	207	176	112	79	79	94	83	171	+67	88		-24	
741	119	173	187	155	148	144	180	180	176	162	+43	167		+19	
833	86	180	205	155	94		Animal killed			156	+70				
Average*	112	186	207	156	110	122	146	149	130	163	+51	135		+25	
										(140)	(+3)	(155)		(+41)	

\* In parentheses are given the normal averages for these animals

TABLE 5—Blood Sugar Curves After the Modified Dextrose Tolerance Test and the Administration of Epinephrine in Rabbits Treated with Thyroxine

Number	Total Dose of Thyroxine in Mg per Kg	Blood Sugar After 5 Gm of Dextrose in 100 Cc of Water and 1 Unit of Insulin						Blood Sugar After 0.1 Mg of Epinephrine					Average Blood Sugar for 3 Hr After Dextrose, 3 Hr and Water and Initial Insulin	Difference Between Average Blood Sugar for 2 Hr After Epine phrine	Difference Between Average Blood Sugar for 3 Hr After Dextrose and 3 Hr Blood Sugar
		Initial Blood Sugar	1/2 Hr	1 Hr	2 Hr	3 Hr	3 1/2 Hr	4 Hr	4 1/2 Hr	5 Hr					
740	5.5	119	114	115	97	151	148	176	184	180	120	+ 1	169	+ 18	
739	6.6	121	151	126	86	144	176	216	220	234	120	— 4	225	+ 81	
751	7.7	173	241	230	122	119	187	241	281	284	173	0	225	+ 107	

almost unchanged in one. The average blood sugar after the administration of epinephrine for three rabbits before fasting was 155 mg, with an increase of 41 mg over the three hour blood sugar, while after starvation it was 135 mg, with an increase of only 20 mg. The peaks of the postepinephrine curves in two cases were also correspondingly lower.

As was expected, the hepatic glycogen of the fasting rabbits (table 3) was low, averaging only 0.76 Gm per hundred grams. After the administration of dextrose, water and insulin similarly to the controls, the glycogen content rose to 2.58 Gm per hundred cubic centimeters.

Microscopic examination of the liver of two rabbits killed after three days of fasting revealed some shrinking of the trabecula with widening of the spaces between. These changes were more marked near the central veins.

*Animals Treated with Thyroxine*—Three rabbits received subcutaneously over a period of five days in equal doses 5.5 mg, 6.6 mg, and 7.7 mg of thyroxine per kilogram of body weight. In spite of an unlimited amount of the usual food in the cages and an apparently excellent appetite, the animals lost during this time between 11 and 15 per cent of their weight. Aside from moderate emaciation, a certain "jumpiness" was the only observed clinical sign.

The data on the blood sugar obtained from these rabbits are given in table 5, while chart 1 shows the curve for the animal that received the largest dose of thyroxine (751). The sugar tolerance of two rabbits that received the smaller doses of thyroxine was found to be practically unchanged. The only remarkable feature of both curves is the abrupt rise of blood sugar between the second and third hours, representing an accentuation of the return to the normal level, which in these cases is as high as the peak of the respective curves. In the third rabbit, the initial blood sugar and the curve during the first hour of the experiment not only exceed the normal values for this animal, but are higher than those for any normal animal in our series. The average blood sugar during the three hours and the increase over the initial blood sugar are also correspondingly higher. On the other hand, the exaggerated return of the blood sugar to the normal level is lacking.

As to the response to epinephrine of the rabbits treated with thyroxine, even within the two hours of observation the average blood sugar was 206 mg, with an increase of 85 mg over the three hour blood sugar, versus 173 mg, with an increase of 68 mg in the same animals when normal. In addition, only the first rabbit showed a small decline in the curve before the end of two hours, while in the other two animals the blood sugar was still on the increase at the end of the experiment. The rabbit treated with the largest doses of thyroxine

exhibited signs of distress following the injection of epinephrine and died during the night

The average glycogen content of the liver in rabbits treated with thyroxine was 0.65 Gm per hundred grams. After the modified dextrose tolerance test, it rose to 2.62 Gm per hundred cubic centimeters (table 3).

Microscopic examination of the livers of two rabbits treated with thyroxine revealed no organic lesions other than shrinkage of the columns of hepatic cells, which was more marked than in those of the fasting animals, and numerous fine brown granules within the cells of the parenchyma.

#### COMMENT

After the administration of dextrose, water and insulin, fasting rabbits showed a diminished sugar tolerance and following injections of epinephrine a less marked rise in blood sugar. Reduction of the sugar tolerance through fasting was discovered by Bang,<sup>4</sup> who attributed it to a reduced ability on the part of the liver to form glycogen. According to Staub,<sup>5</sup> fasting leads to inhibition of the formation of insulin and thus retards the utilization of sugar. Finally, Elias<sup>6</sup> advanced the theory that acidosis due to hunger is responsible for the diminished sugar tolerance through slower formation of glycogen and retardation of absorption of sugar by the tissues. Van Noorden and Isaac<sup>7</sup> modernized the theory of Bang by the supposition that the formation of glycogen in the liver is dependent on the existing supply of glycogen in this organ from which energy for the polymerization of dextrose is derived through its transformation into lactic acid. In addition, they concede the possibility of a temporary insufficiency of insulin as a contributing factor.

In the present experiment, the glycogen content of the normal liver after the administration of dextrose, water and insulin was found to be about 50 per cent higher than that of the controls. In the fasting group, the amount of hepatic glycogen after the modified dextrose tolerance test was three times as great as that in the fasting controls. The absolute increase in glycogen amounted to 2.7 Gm per hundred grams of hepatic tissue in the normal rabbits and to only 1.6 Gm in the fasting animals. Since the possible insufficiency of insulin in this experiment was counteracted by exogenous insulin, it appears that

4 Bang, J. *Der Blutzucker*, Wiesbaden, J. F. Bergmann, 1913.

5 Staub, H. *Untersuchungen über den Zuckerstoffwechsel des Menschen*, *Ztschr. f. klin. Med.* **91** 44, 1921, *ibid.* **93** 89, 1922.

6 Elias, H. *Zur Bedeutung des Säurebasenauflages und seiner Störungen*, *Ergebn. d. inn. Med. u. Kinderh.* **25** 192, 1924.

7 von Noorden, G., and Isaac, S. *Die Zuckerkrankheit und ihre Behandlung*, Berlin, Julius Springer, 1927, p. 33.

diminution of the existing supply of hepatic glycogen in fasting animals is at least in part responsible for the slower deposition of glycogen in the liver, which in its turn makes for a reduced sugar tolerance

Diminution of the response to epinephrine in the fasting rabbits was in all probability caused by a low glycogen content of the liver. It is true that recent experiments by Cori and Cori<sup>8</sup> tend to show that other factors such as reduced utilization of blood sugar by the tissues, may enter into the production of hyperglycemia after the administration of epinephrine, yet the work of Sahyun and Luck<sup>9</sup> demonstrated anew that mobilization of hepatic glycogen is an important part of the action of this hormone, at least during the first two hours after the injection

Deviations from the normal of blood sugar curves observed in three rabbits treated with thyroxine are in accord with the work of Burn and Marks,<sup>10</sup> and of Marks<sup>11</sup>. The exaggerated return of the blood sugar to normal in the first two animals is due to the fact that thyroxine renders the liver overresponsive to stimuli that promote a discharge of sugar into the blood. In this case such a stimulus was provided by lowering of the blood sugar. On the other hand, this overactivity of the liver can find expression only in the presence of a certain minimum of glycogen in this organ. Therefore this phenomenon is absent in the case of the third rabbit, which received the largest dose of thyroxine.

The normally shaped but very high three hour blood sugar curve of the same animal is caused by a decrease of the hypoglycemic reaction to insulin typically produced by the administration of thyroid extract over a certain length of time. Finally, the increased hyperglycemia after the administration of epinephrine is explained by sensitization of the liver to this hormone as already observed by the authors mentioned. It is of interest that the increased reaction to epinephrine in our experiment was produced by smaller doses of thyroxine than were necessary to bring about a decrease in the response to insulin.

The average glycogen content of the liver of rabbits treated with thyroxine was slightly below that of the fasting animals, and the hepatic glycogen after the administration of dextrose, water and insulin showed approximately the same increase. This similarity in regard to the

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8 Cori, C. F., and Cori, G. T. The Mechanism of Epinephrine Action, Influence of Epinephrine on Carbohydrate Metabolism of Fasting Rats, with Note on New Formation of Carbohydrates, *J. Biol. Chem.* **79** 309 (Sept.) 1928, Mechanism of Epinephrine Action, Influence of Epinephrine and Insulin on Carbohydrate Metabolism of Rats in Postabsorptive State, *ibid.* **79** 321

9 Sahyun, M., and Luck, J. M. The Influence of Epinephrine and Insulin on the Distribution of Glycogen in Rabbits, *J. Biol. Chem.* **85** 1, 1929

10 Burn, J. H., and Marks, H. P. The Relation of the Thyroid Gland to the Action of Insulin, *J. Physiol.* **60** 131, 1925

11 Marks, H. P. Effect of Thyroid Feeding on Sugar Tolerance, *J. Physiol.* **60** 402, 1925

accumulation of glycogen in two sets of animals in which reduction of hepatic glycogen was accomplished in such different ways is of considerable interest in view of the very dissimilar blood sugar curves obtained for the two groups

Neither in rabbits in which the glycogen of the liver was reduced by fasting, nor in animals in which the same object was accomplished with injections of thyroxine did the blood sugar curves show the characteristic hypoglycemia observed in persons suffering from diseases of the liver. From this it seems improbable that the described disturbance of the carbohydrate-regulating mechanism in man is caused by lowering of hepatic glycogen. We find clinical confirmation of this conclusion in the observation that patients with diabetes, a disease in which the glycogen of the liver is always reduced, do not show hypoglycemia curves after the modified dextrose tolerance test except when other evidence of hepatic insufficiency is present

#### SUMMARY

Normal, fasting rabbits treated with thyroxine were subjected to a modification of the dextrose tolerance test followed by an injection of epinephrine. Blood sugar curves following these procedures and determinations of the hepatic glycogen before and after the modified dextrose tolerance test were made

The fasting animals were found to have reduced tolerance to sugar and diminished response to epinephrine, both apparently due to a lowered glycogen content of the liver. The rabbits treated with thyroxine showed increased susceptibility to glycogenolytic stimuli and a decrease of hepatic glycogen

In neither of these two groups did the lowering of the glycogen content of the liver produce the hypoglycemia so typical in patients with hepatic diseases after the modified dextrose tolerance test

All rabbits showed an increase in the hepatic glycogen after the administration of dextrose, water and insulin

# INFLUENCE ON CARBOHYDRATE METABOLISM OF EXPERIMENTALLY INDUCED HEPATIC CHANGES

## II PHOSPHORUS POISONING

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In order to produce a diffuse injury of the hepatic parenchyma with as little damage as possible to other organs, the two classic poisons phosphorus and chloroform were used. Anatomically, phosphorus, according to Mosiman and Whipple,<sup>1</sup> attacks chiefly the cell protoplasm. The lesions produced by moderate phosphorus poisoning consist of fatty degeneration, which is described by Opie and Alford<sup>2</sup> as usually appearing in the early stages in the center of the lobules, while later it is most conspicuous near the portal spaces. Severe poisoning by phosphorus produces coagulative necrosis, which has a tendency to be at the periphery of the lobules.

Phosphorus may produce fatty degeneration of a moderate degree also in other organs. However, to quote from an article on the hepatic factor in chloroform and phosphorus poisoning by Williamson and Mann,<sup>3</sup> "The liver is the most seriously damaged organ histologically and physiologically." Opie and Alford, on the basis of their work, came to similar conclusions.

## CHRONIC PHOSPHORUS POISONING

Phosphorus was given in all our experiments by subcutaneous injections in the form of 0.5 per cent solution in oil. In some preliminary

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1 Mosiman, R. E., and Whipple, G. H. Chloroform Poisoning, *Bull. Johns Hopkins Hosp.* **23**: 323 (Nov.) 1912.

2 Opie, E. L., and Alford, L. B. Diet and the Hepatic Lesions of Chloroform, Phosphorus, or Alcohol, *J. Exper. Med.* **21**: 1, 1915.

3 Williamson, C. S., and Mann, F. C. Studies on Physiology of Liver. The Hepatic Factor in Chloroform and Phosphorus Poisoning, *Am. J. Physiol.* **65**: 267, 1923.

experiments, daily doses of 1 mg of phosphorus per kilogram of body weight resulted in the death of the animal within five days. The dose was then reduced to 0.85 mg and produced a fatal outcome in nine days. Finally, 0.75 mg of phosphorus per kilogram was chosen as the daily dose, and was employed in eight rabbits. Of these animals two died after twelve injections, one succumbed to thirteen doses, and one survived fifteen injections. Two rabbits were killed after ten injections, and two were used for recovery experiments with temporary withdrawal of phosphorus following nine and ten injections, respectively.

On these chronically poisoned rabbits blood sugar curves were made following the administration of dextrose, water and insulin, and also after epinephrine, beginning with the fifth day<sup>4</sup>. The results of the numerous experiments are reported in separate protocols for each animal (table 1), and in addition, the average figures for the various stages are shown in table 2. Figures for the glycogen content of the livers of these animals before and after the modified dextrose tolerance test are given in table 3.

*Results*—Four Day Stage. In two rabbits examined four days after the beginning of the injections of phosphorus, the initial blood sugar was found to be lowered. The peak of the curves was at the normal period, but the two hour blood sugar was high. The average blood sugar was somewhat lower than that of the same animals when normal, but the increase over the initial level was marked. The epinephrine response in these rabbits was almost two times greater than normal, whether judged by the average blood sugar or by the peak of the curve. The hepatic glycogen in two rabbits was reduced to 0.6 per cent.

Six Day Stage. In three animals tested on this day the findings were essentially similar to those found at the preceding stage. The hyperglycemia after epinephrine was greater than normal in two rabbits and lower in one. The highest blood sugar in all three curves following epinephrine was observed in the last specimen.

Eight Day Stage. In two animals at this phase of the action of phosphorus, in addition to a low initial blood sugar and a lower average blood sugar with a greater increase over the initial level, the peak of the curve after the administration of dextrose, water and insulin was found at the one hour period. Likewise the epinephrine response was below normal, coincident with a drop of the curve during the first half hour after the injection. The maximum blood sugar after the use of this hormone was again reached at the end of two hours.

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4 For description of methods see our first paper, "The Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes. I. Fasting and Thyroxine Administration," *Arch. Ind. Med.*, this issue, p. 46.



TABLE 1—Blood Sugar Curves After the Modified Dextrose Tolerane Test and the Administration of Epinephrine in Rabbits Subjected to Chronic Phosphorus Poisoning

[illegible]

[illegible]

\* 1½ hour curve without epinephrine having been given

† Sodium lactate only administered

TABLE 2.—*Significant Average Blood Sugar Figures After the Modified Dextrose Tolerance Test and the Administration of Epinephrine in the Group with Chronic Phosphorus Poisoning*<sup>1</sup>

Days After Poisoning	Number of Rabbits	Blood Sugar After 5 Gm. of Dextrose in 100 Cc. of Water and 1 Unit of Insulin					Blood Sugar After 0.1 Mg. of Epinephrine				
		Initial Blood Sugar	Peak of Curve	Difference Between Initial Blood Sugar and Peak	Average Blood Sugar for 3 Hr	Difference Between Average and Initial Blood Sugar	3 Hr Blood Sugar	Peak of Curve	Difference Between Peak and 3 Hr Blood Sugar	Average Blood Sugar After Epi nephrine	Difference Between Average Blood Sugar for 2 Hr and 3 Hr
4	2	112 (151)	178 (186)	+66 (+35)	133 (149)	+21 (- 2)	103 (126)	197 (189)	+94 (+57)	161 (159)	+53 (+33)
6	3†	120 (137)	153 (168)	+33 (+31)	131 (136)	+11 (- 1)	118 (116)	214	+96	116	+48
6	2						105 (126)	186 (189)	+81 (+57)	153 (159)	+48 (+33)
8	2	99 (131)	162 (186)	+63 (+35)	121 (149)	+22 (- 2)	94 (126)	142 (189)	+49 (+57)	109 (159)	+15 (+33)
9	2	103 (127)	186 (157)	+83 (+30)	153 (115)	+50 (-12)	146 ( 87)	150	+ 4	143	- 3
10	6†	93 (136)	164 (170)	+71 (+34)	135 (128)	+12 (- 8)	89 ( 98)	112	+23	98	+ 9
10	2†						79 (108)	112 (201)	+33 (+93)	96 (146)	+17 (+56)
No epinephrine response	6	92 (133)	168 (170)	77 (+37)	138 (120)	+46 (- 7)	106 ( 97)	99	- 7	91	-15
No epinephrine response	2†						95 (108)	83 (201)	-12 (+93)	76 (164)	-19 (+56)

\* Parentheses indicate the normal average figures for the rabbits

† Blood specimens corresponding to the first three hours of one curve were not obtained

‡ Animals for which post epinephrine curve had been made before poisoning

**Nine Day Stage** Two rabbits examined on this day exhibited to an increased degree all the abnormalities of the three hour curve previously mentioned, and the average blood sugar became higher than that in the normal animals. Furthermore, the maximum elevation of blood sugar was observed in one rabbit at the two hour period. The effect of epinephrine in one case was slight, while in the other a steady falling off of the curve was observed. The average blood sugar in the second rabbit following administration of epinephrine was 15 mg lower than at the time of injection.

**Ten Day Stage** Six animals were tested at this stage. Blood sugar curves of the modified dextrose tolerance test were essentially similar to those of the previous day, only now the peak of the curves was

TABLE 3—*Glycogen Content of the Liver in Rabbits Poisoned with Phosphorus Before and After the Modified Dextrose Tolerance Test*

Chronic Phosphorus Poisoning 4 Days		Chronic Phosphorus Poisoning, No Response to Epinephrine				Acute Phosphorus Poisoning 14 Hour Stage			
Before Administration of Dextrose, Water and Insulin		Before Administration of Dextrose, Water and Insulin		After Administration of Dextrose, Water and Insulin		Before Administration of Dextrose, Water and Insulin		After Administration of Dextrose, Water and Insulin	
Num ber	Glyco gen, per Cent	Num ber	Glyco gen, per Cent	Num ber	Glyco gen, per Cent	Num ber	Glyco gen, per Cent	Num ber	Glyco gen, per Cent
748	0.5	0	0.3	828	0.5	839	4.01	817	3.42
774	0.7	826	1.9	831	0.3			819	1.30
		904	0.9						
Average, Animals per Cent		Average, Animals per Cent		Average, Animals per Cent		Average, Animals per Cent		Average, Animals per Cent	
2	0.6	3	1.0	2	0.4	1	4.01	2	2.36

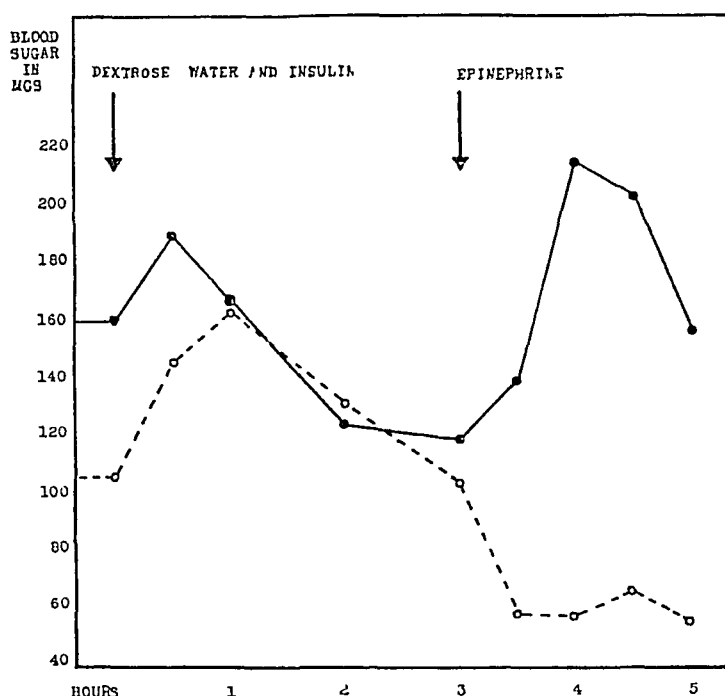
observed at the two hour period in three rabbits. Hypoglycemic curves after the administration of epinephrine were encountered in four cases, and both reduced and delayed responses were found in two cases.

**Later Stages** One of the last two rabbits (741) that had the greatest resistance to phosphorus showed a still further reduced response to epinephrine on the thirteenth day and a deep hypoglycemic curve after the administration of this hormone when tested on the sixteenth day of progressive poisoning. Animal 816 had no hypoglycemia after the administration of epinephrine at the thirteen day stage, and was found dead on the morning of the sixteenth day. Finally, a third rabbit (735) had a low epinephrine curve at the eight day stage, and died on the fifteenth day without having been tested again.

Average blood sugar figures for six rabbits that had lost their response to epinephrine are given for convenience at the end of table 2, and a typical blood sugar curve is reproduced in the accompanying

chart All eleven curves at the stage under discussion are characterized by lowering of the blood sugar half an hour following the injection of epinephrine

After reaching the stage of phosphorus poisoning in which post-epinephrine hyperglycemia is lacking, the rabbits were either killed for analysis of the liver or were used for special experiments On one of the latter animals (833), which was used for a recovery experiment and later again given phosphorus, it was possible to make a complete curve one hour before death The blood sugar level in this rabbit during the first three hours was very low, but the average blood sugar was still higher than the initial value in contrast to the normal curve



A typical blood sugar curve of a rabbit (741) after the modified dextrose tolerance test and the administration of epinephrine A late stage of chronic phosphorus poisoning is shown by the broken line, the solid line traces the curve obtained previous to poisoning

of the same animal The curve after the administration of epinephrine was of the usual hypoglycemic type

The glycogen content of the livers of three rabbits that lost their response to epinephrine varied between 0.3 per cent and 1.9 per cent, averaging 1 per cent After the administration of dextrose, water and insulin, the hepatic glycogen in two such animals amounted to only 0.4 per cent

*Special Experiments*—1 Five Hour Sugar Tolerance Curves Without Epinephrine In order to ascertain whether the hypoglycemia after

the administration of epinephrine was actually caused by this hormone or took place in spite of it, five hour blood sugar curves following the administration of dextrose, water and insulin were obtained in two rabbits in which the epinephrine response was no longer present. In one of these animals (831) the typical hypoglycemic curve was obtained. The other rabbit (833), in which injections of phosphorus had been discontinued two days before, also had a very low curve, but beginning recovery was manifested by a rise of the blood sugar in the last specimen.

2 Utilization of Lactic Acid in Phosphorus Poisoning. During experiments with the Warburg apparatus, Meier and Thoenes<sup>5</sup> made the observation that when to normal hepatic tissue a solution of racemic sodium lactate was added the respiratory quotient decreased, presumably because in the process of formation of dextrose the sodium ions are liberated and are free to combine with carbon dioxide. On the contrary, in similar experiments with livers from guinea-pigs treated with phosphorus the respiratory quotient remained unchanged. From this point of view it seemed interesting to follow the blood sugar of normal and poisoned rabbits after the administration of tolerance doses of lactic acid.

Lactic acid was given by stomach tube in the form of sodium lactate solution obtained by neutralization of normal lactic acid with 30 per cent sodium hydroxide. The dose was 2 Gm per kilogram of body weight, the largest amount tolerated by rabbits without causing a rise of blood sugar, according to the work of Cori and Cori.<sup>6</sup>

These experiments were carried out on two animals. In rabbit 833 a three hour blood sugar curve after sodium lactate showed no rise of the blood sugar above the initial level. The average blood sugar during this time was 8 mg lower than that taken before the administration of sodium lactate. When the toxic stage was reached, characterized by hypoglycemia during the last two hours of the tolerance test, the experiment was repeated. This time there was a moderate rise in the curve after sodium lactate, and the average blood sugar was 10 mg above the initial value.

In a second rabbit (831) the first experiment with sodium lactate was performed as soon as the animal regained its ability to react to epinephrine after the administration of phosphorus was discontinued. This curve again showed practically no rise over the initial level and an average blood sugar that was 4 mg below that at the beginning of the test. Injections of phosphorus were resumed, and three days later a curve after the administration of sodium lactate was obtained. This

<sup>5</sup> Meier, R., and Thoenes, E. Unpublished experiments.

<sup>6</sup> Cori, C. F., and Cori, G. T. Glycogen Formation in the Liver From D- and L- Lactic Acid, *J. Biol. Chem.* **81** 389, 1929.

curve exhibited considerable hyperglycemia, with its peak at the one hour period and elevation of the average blood sugar over the initial value amounting to 32 mg. The response to epinephrine at this time was reduced but still present. Two days later the experiment was done again, with the result that a similar hyperglycemic curve was observed, which had its peak at the three hour period. The average blood sugar was 30 mg. above the initial level. The corresponding curve after the administration of epinephrine this time showed hypoglycemia.

**3 Recovery Experiments** On four occasions in three rabbits the administration of phosphorus was discontinued after hypoglycemia had appeared in the second part of the curve. In one of these animals (831) the hyperglycemia after the administration of epinephrine reappeared once after one day and once after two days of rest from injections of phosphorus. Another rabbit (833) regained its capacity to react to this hormone in two days. In the third animal (741) the hypoglycemia was markedly lessened after two days. Coincidentally, the three hour blood sugar curves, which were made only for the two last animals, showed their peaks again at the half hour period as normally. As additional signs of recovery in the second rabbit, the initial blood sugar had increased, the blood sugar level at the two and three hour periods had become lower than the initial blood sugar, and the average blood sugar was reduced.

When the injections of phosphorus were renewed, the typical hypoglycemia reappeared after a single injection in the animal in which only one injection was left out. In the rabbits in which two consecutive doses of phosphorus were omitted it required, respectively, nine and thirteen injections before the characteristic hypoglycemia was again observed.

*Pathologic Data*—The livers of two rabbits (748 and 774) killed after four daily doses of phosphorus (corresponding to the first stage of our observations) were examined, and fatty degeneration of the cells around the portal spaces was found extending about half way to the central veins. Furthermore, in one of these animals hyaline cells were scattered irregularly through the lobules.

Livers of four animals at the terminal stage were examined microscopically. Two of these (740 and 828) were killed after having shown a hypoglycemic curve, and two (735 and 816) died spontaneously. The histologic picture of all four livers was essentially alike. There was very little fat present, but that small amount was diffusely scattered in small droplets. Most parenchyma cells were very young and exhibited evidence of rapid proliferation. They were irregularly placed without the usual trabecular arrangement. The nuclei showed no degeneration.

Finally, one rabbit (741) that died nine days after the last dose of phosphorus showed the same microscopic appearance of the liver and, moreover, marked congestion of the whole parenchyma with extravasation of blood around the central veins

#### ACUTE PHOSPHORUS POISONING

As a check on certain phases of the work with chronic phosphorus poisoning several rabbits were given single doses of 4.5 mg of phosphorus per kilogram of body weight. Two of these rabbits were alive twenty-four hours later, but were found dead thirty-six hours after the injection. Two more animals were killed for observations on the hepatic glycogen. Three of the rabbits that received single large doses of phosphorus were subjected fifteen hours later to the sugar tolerance and epinephrine tests. The obtained data are given in table 4. Figures

TABLE 4—*Blood Sugar Curves after the Modified Dextrose Tolerance Test and the Administration of Epinephrine to Rabbits Subjected to Acute Phosphorus Poisoning*

No	Blood Sugar After 5 Mg of Dextrose in 100 Cc of Water and 1 Unit of Insulin					Blood Sugar After 0.1 Mg. of Lpi nephrene				Average Blood Sugar for 3 Hr After Dextrose, Water and Insulin	Difference Between Average Blood Sugar for 3 Hr and the Initial Count	Average Blood Sugar for 2 Hr After Epi nephrene	Difference Between Average Blood Sugar for 2 Hr and 3 Hr
	Ini tial	1/2 Hr	1 Hr	2 Hr	3 Hr	1/2 Hr	1 Hr	1 1/2 Hr	5 Hr				
803	86	90	72	76	65	47	51	32	36	77	— 9	46	— 19
811	122	209	220	140	137	392	338	367	346	170	+ 18	335	+ 198
819	108	119	148	110	108	Animal killed				131	+ 23		

on the glycogen content of the liver before and after the modified dextrose tolerance test are given in table 3. From this it is seen that the initial blood sugar in all three rabbits was markedly lowered. In one animal (811) the three hour curve showed a remarkable hyperglycemia. In another rabbit (819) the average blood sugar level was also considerably higher than the initial value. In the third animal (803) there was practically no elevation of the blood sugar after dextrose, water and insulin had been given, and the average blood sugar was very low. But the difference between the latter and the initial blood sugar was the same as before poisoning. In the two curves in which the elevation of blood sugar took place, the peaks were at the one hour period, and the two hour blood sugar was above the initial one.

After epinephrine the blood sugar in the first animal rose in thirty minutes from 137 mg to a maximum of 392 mg and remained very high. Conversely, in the third rabbit the blood sugar fell to a very low level (32 mg) and remained low, without causing convulsions.



The hepatic glycogen in one rabbit was found to be 4 per cent. After administration of dextrose, water and insulin it averaged 2.36 per cent in two animals.

*Pathologic Examination*—Two rabbits in this series were examined pathologically, fifteen and eighteen hours, respectively, after the injection of phosphorus. Histologically, the liver of animal 817 showed nothing abnormal except vascular engorgement, while that of 819 exhibited beginning diffuse fatty infiltration which was most marked a little distance from the portal spaces. The livers of two rabbits that were found dead thirty-six hours after the injection were also studied. In one animal (803) extensive fatty degeneration involved most of the lobules except two or three rows of cells surrounding the central veins, where the fat droplets were less numerous. In addition, the parenchymatous cells were hyalinized and often exhibited pyknotic nuclei. The liver of animal 811 presented a picture of widespread necrosis with hemorrhages involving the entire parenchyma but leaving a thin fringe of intact cells around the portal spaces. All cells were heavily laden with fat.

#### COMMENT

*Chronic Phosphorus Poisoning*—In considering the significance of these experimental findings two facts must be constantly borne in mind. The first is that the principal function of the liver in its relation to carbohydrate metabolism, as emphasized by Fischler,<sup>7</sup> is the maintenance of a constant blood sugar level. The second is that while practically all investigators of the action of phosphorus and chloroform concur in the opinion that the liver is the only organ seriously damaged by these substances, there are other factors concerned in the utilization of carbohydrates which, by exercising a compensatory function in hepatic insufficiency, may modify the effect of injury to the liver without direct action of these poisons on other organs.

In reviewing the influence of chronic phosphorus poisoning on rabbits, we see that as early as four days after the beginning of injections of phosphorus the initial blood sugar and the glycogen content of the liver were considerably lowered. Thereafter, the initial blood sugar remained low until death. In other words, from the beginning evidence points to a deficiency of the chief function of the liver, that of maintaining a certain optimum blood sugar level. The same observation was made by Mann<sup>8</sup> on dogs with partial hepatectomies. Drastic lowering of the blood sugar level after phosphorus poisoning in man

7 Fischler, F. *Physiologie und Pathologie der Leber*, Berlin, Julius Springer, 1925, p. 65.

8 Mann, F. C. *The Effects of Complete and Partial Removal of the Liver*, *Medicine* 6: 420 (Dec.) 1927.

was reported by McIntosh<sup>9</sup> and by McLean, MacDonald and Sullivan<sup>10</sup> Experimental results that conflict with ours may be explained, at least in cases in which rabbits were used, as suggested in our preliminary experiments, by lowering of the blood sugar in the controls through over-night fasting

As poisoning with phosphorus progressed, the sugar tolerance of our rabbits was gradually reduced In reference to the shape of the curve, the manifestations of diminution in dextrose tolerance on the fifth day were a relatively higher peak at the normal time and a slower return of the blood sugar to the initial level On the ninth day the blood sugar continued to rise during the entire first hour, and on the eleventh day in three of the six rabbits the blood sugar reached its maximum only at the two hour period

Quantitatively, up to the ninth day of poisoning the average blood sugar for three hours was below normal, due to the low initial blood sugar level, but the increase of the average blood sugar over the initial level was considerably greater than the normal for the same animals From the tenth day on, both the average and, more strikingly, the increase of the average over the blood sugar at the beginning of the test were greater than before the administration of phosphorus The explanation for this reduced sugar tolerance is at least partially supplied by the fact that the glycogen content of the livers of these animals is somewhat reduced instead of being increased after administration of dextrose, water and insulin

The work of Mann and Bollman<sup>11</sup> with partial hepatectomies shows that reduced capacity of the liver can be responsible for a delayed rate of disappearance of sugar from the blood Von Noorden and Isaac,<sup>12</sup> among others mentioned the higher and more prolonged rise of the blood sugar after the administration of dextrose in patients with hepatic disease It must be remarked here that the last observation holds true only for group averages In many cases of even advanced diseases of the liver, the sugar tolerance is found to be still within the upper limits of normal On the other hand, in the present study injury to the pancreas and voluntary fasting by the indisposed animals must be ruled out as possible causes of reduced sugar tolerance

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9 McIntosh, R M Acute Phosphorus Poisoning, *Am J Dis Child* **34**: 595 (Oct) 1927

10 McLean, S A, MacDonald, A, and Sullivan, R C Acute Phosphorus Poisoning from the Ingestion of Roach Paste, *J A M A* **93** 1989 (Dec 7) 1929

11 Mann, F C, and Bollman, J L Liver Function Tests, *Arch Path & Lab Med* **1** 681 (May) 1926

12 von Noorden, C, and Isaac, S Die Zuckerkrankheit und ihre Behandlung, Berlin, Julius Springer, 1927, p 42

Besides the histologically demonstrated relative immunity of the pancreas to phosphorus, the uniformly low initial blood sugar in all stages of poisoning speaks strongly against any considerable damage of this organ in our rabbits. The hypoglycemia that commences three and one-half hours following the modified dextrose tolerance test, when a certain stage of phosphorus poisoning is reached, also argues against an insufficiency of insulin.

The possibility that voluntary fasting lowered the sugar tolerance of the rabbits appears unlikely, because, except for the last two or three days before death, the animals showed no change in their habits of eating. Moreover, a similar decrease of sugar tolerance was observed in our acute experiments when the animals were tested twelve hours after the injection of a large dose of phosphorus. It is evident that under these conditions fasting played no part.

Observations on a rabbit (833) in the most advanced stage of phosphorus action showed very little rise in blood sugar after the administration of dextrose, water and insulin given six hours before death. However, the average blood sugar in contrast to that found in the same animal in the normal state was still higher than the initial blood sugar. This terminal increase in sugar tolerance, if real, has its counterpart in the greater rate of disappearance of dextrose injected into totally dehepatized dogs and is interpreted by Mann and Bollman<sup>11</sup> as being due to loss of the regulatory action of the liver. On the other hand, in our animal it might also have been caused by poor absorption from the alimentary canal in view of impending dissolution.

The epinephrine hyperglycemia of our rabbits was greatly increased four days after the beginning of injections of epinephrine. Two days later it was still increased, but less in two animals, and it was decreased in one. In addition, there was at this stage in all animals a delay in the action of epinephrine, as shown by curves that reached their peaks in the last blood sample. On the ninth day the response to epinephrine was below normal, and the delay of its action had found additional expression in a continuation of the fall in blood sugar during the first thirty minutes after the injection.

Starting on the tenth day of poisoning in one rabbit, on the eleventh day in four and on the sixteenth day in another, no increase but a fall in blood sugar after the administration of epinephrine took place (see the accompanying chart). Two rabbits died without having been observed in this hypoglycemic stage. One of these (735) had only a slight epinephrine hyperglycemia on the ninth day and died six days later without further tests having been made. The other animal (816) exhibited reduced and delayed response to epinephrine on the eleventh day, and succumbed two days later without further observations having been made. In both rabbits daily injections of phosphorus were con-

tinued until death, and it is highly probable that the characteristic hypoglycemia was missed, because no tests were made during the last days of life

Two of the six rabbits (831 and 833) for which the hypoglycemic curves after the injection of epinephrine had been observed were permitted to recover, the injections of phosphorus being stopped. When poisoning was resumed, both animals again exhibited lowering of the blood sugar following the administration of epinephrine.

From the observed facts it is seen that at first small doses of phosphorus act as an irritant to the glycogenolytic mechanism of the liver and similarly to thyroxine, rendering the liver more susceptible to the action of epinephrine in spite of a marked reduction in hepatic glycogen. This phase of our study confirms the conclusion that Macleod<sup>13</sup> drew from the results of experiments with thyroxine "that it is not alone the percentage of glycogen in the liver that determines the readiness with which this organ may discharge sugar into the blood, but also the sensitivity of the glycogenolytic mechanism." Whipple, Peigntal and Clark,<sup>14</sup> who reported hypersecretion of phenoltetrachlorophthalein by the liver after small doses of phosphorus, also looked for an explanation to the irritative effect of this drug on the secreting parenchyma—a stage perhaps preceding that of actual injury or necrosis of the cells.

For better understanding of this phenomenon, it was necessary to determine whether the hypoglycemia described, which was observed in eleven curves made for six rabbits, was caused by epinephrine or whether it took place in spite of it. Observations of the blood sugar over five hours with the modified dextrose tolerance test without epinephrine being given in two rabbits (831 and 833) showed that epinephrine was not responsible for the hypoglycemia. On the other hand, this hormone was impotent to prevent its occurrence or even to diminish it.

Mann and Magath<sup>15</sup> demonstrated that extirpation of the liver prevented hyperglycemia after the administration of epinephrine, and that there was not even a temporary delay in the steady fall of blood sugar in dogs. In demonstrating the dependence of post-epinephrine hyperglycemia on the functional activity of the liver, the present experiments possess the advantage that the action of epinephrine was abolished

13 Macleod, J. J. R. The Physiology of Glycogen and the Role of Insulin and Epinephrine in Carbohydrate Metabolism, *Lancet* **2** 1 (July 6) 1929.

14 Whipple, G. H., Peigntal, T. C., and Clark, A. H. Tests for Hepatic Function and Disease Under Experimental Conditions, Phenoltetrachlorophthalein, *Bull. Johns Hopkins Hosp.* **24** 343 (Nov.) 1913.

15 Mann, F. C., and Magath, T. B. Die Wirkungen der totalen Leberextirpation, *Ergebn. d. Physiol.* **23** 212, 1924.

in rabbits in which the blood sugar following a period of hypoglycemia was able to return spontaneously to its previous level, and that the animals in which this occurred were still capable of prompt recovery at the cessation of injections of phosphorus

The fact that phosphorus poisoning prevents the hyperglycemic action of epinephrine is difficult to reconcile with the view that decreased utilization of blood sugar by the tissues is the principal cause for hyperglycemia after the administration of this drug under postabsorptive conditions. If this were true, why should hepatic damage in animals in the postabsorptive stage nullify the action of epinephrine?

The genesis of the hypoglycemia that occurred so regularly at a certain stage of phosphorus poisoning is especially interesting to us because of its similarity to the hypoglycemia observed in human cases of hepatic disease following the modified dextrose tolerance test. We know that the main mechanism by which a nearly constant blood sugar level is maintained in the normal animal is the secretion of insulin, which increases the utilization of sugar by tissues when hyperglycemia begins to appear, and the release of dextrose from the glycogen stores of the liver when a certain degree of hypoglycemia is reached. This balance is demonstrated in the ordinary dextrose tolerance test by a fall of the blood sugar curve below the initial level toward the end of the test and by a secondary rise which follows this fall.

In late phosphorus poisoning the ability of the liver to release dextrose is abolished, as was demonstrated by the experiments with epinephrine. In consequence, the downward course of the blood sugar continues unchecked until the stimulus furnished by the dextrose absorbed from the intestine is exhausted. In this manner marked hypoglycemia is produced following the initial hyperglycemia. The injection of insulin and the administration of water along with the feeding of dextrose in the modified dextrose tolerance test intensify this fall in blood sugar. In addition, it is probable that with the onset of hepatic insufficiency the tissues and the pancreas take a larger part in the disposal of absorbed carbohydrates, thus increasing still further the tendency to terminal hypoglycemia.

Before we leave the subject of chronic phosphorus poisoning, it seems interesting to point out the comparatively normal appearance of the hepatic cells and the slight amount of fatty degeneration in the livers of rabbits that died or were killed in advanced stages of poisoning. This is the more unexpected since in earlier stages fatty degeneration is pronounced. The only important abnormalities of the liver found in late stages of chronic phosphorus poisoning are the loss of trabecular arrangement of the parenchymatous cells and their young appearance.

*Acute Phosphorus Poisoning*—The results of the experiments with single large doses of phosphorus are confusing when taken alone, but

easily interpreted when viewed in the light of the changes produced by chronic poisoning. The initial blood sugar was lowered in all three rabbits. The two three hour curves that rose after the modified tolerance test are both indicative of reduced sugar tolerance. The third curve obtained in rabbit 803 which had lost its response to epinephrine is similar to the tolerance curve obtained shortly before death in the chronically poisoned animal 833. The epinephrine hyperglycemia was extreme in one case (811), indicating a short stage of nutrition similar to the more protracted one in the animals subjected to chronic poisoning. The fact that the maximum elevation of the blood sugar was reached thirty minutes after the injection of epinephrine is additional proof of the lability of the glycogenolytic mechanism in this rabbit. The other animal (803), for which a post-epinephrine curve was obtained, already showed the typical hypoglycemia and lack of response to this hormone so characteristic of later stages of poisoning with small doses of phosphorus. Finally, the glycogen content of the liver was reduced, although to a lesser extent, and administration of dextrose, water and insulin, just as in chronic phosphorus poisoning, brought about a reduction, rather than an increase, in hepatic glycogen.

One may conclude from these observations that acute and chronic poisoning with phosphorus produce the same effects on sugar tolerance and epinephrine response. Since in the acute experiments the sequence of events is much faster, different degrees of functional impairment (depending on the rate of absorption of phosphorus, susceptibility of the individual animal, etc.) may be observed after the same number of hours following the injection of the poison. Individual differences in function found their counterpart in variations in the histologic picture observed in the livers of rabbits killed at the same period after the administration of equal doses of phosphorus.

*Utilization of Lactic Acid in Phosphorus Poisoning*—Experiments with feeding of sodium lactate demonstrated that in advanced stages of phosphorus poisoning hyperglycemia is produced with amounts of sodium lactate that were previously tolerated without elevation of the blood sugar. Moreover, the peak of the hyperglycemic curve fell into a later period as poisoning progressed, just as after tolerance tests with dextrose. These results indicate that lactic acid is still converted into dextrose after the liver becomes unable to release a sufficient amount of sugar from glycogen in response to the stimulus of hypoglycemia and of epinephrine. However, the dextrose produced is subject to the same delayed utilization as the sugar absorbed from the gastro-intestinal tract.

The fact that the liver retains its capacity to change lactic acid into dextrose in late stages of phosphorus poisoning permits the cycle of blood sugar  $\rightarrow$  muscle glycogen  $\rightarrow$  lactic acid  $\rightarrow$  blood sugar to continue

even in the apparent absence of glycogen formation. This and probably dextroogenesis explain the survival of our rabbits during the last stage of this experiment and also furnish a key to the understanding of the mechanism by which the low blood sugar induced by the modified tolerance test slowly returned to its previous level after failing to show an increase following the injections of epinephrine.

*Recovery from Phosphorus Poisoning*—The prompt recovery of the rabbits when administration of the phosphorus was discontinued testifies that neither the hypoglycemia during the second half of the five hour curve nor the absence of the epinephrine response can be regarded as a terminal event in fatal cases of poisoning. So far as can be judged from the limited number of observations, hyperglycemia after the administration of epinephrine was the first condition to return in the recovering animals. Sugar tolerance and especially the initial blood sugar level were somewhat slower to recover.

After the administration of phosphorus was discontinued, the animals acquired resistance to further injections of this poison with extraordinary rapidity. When a single injection of phosphorus had been omitted, the injection following abolished the response to epinephrine. But when two injections were left out in one rabbit (833) it took as many, and in another case (831) even one and one-half times as many, injections as were required for the healthy animals in order to reach the same stage. Since we know from our tests of sugar tolerance and epinephrine response that the rabbits had not completely recovered when the second period of poisoning was started, it seems probable that the new cells of the liver at this particular stage were more resistant to phosphorus. This impression is also strengthened by the virtual absence of fatty degeneration in the young cells. It is of interest that Davis and Whipple<sup>16</sup> had the same experience in dogs with a temporary tolerance to chloroform immediately after recovery from the first dose. When the animals in their series were allowed to recuperate for two or three weeks, a tolerance to the second dose was not exhibited.

#### SUMMARY

Rabbits receiving small daily doses of phosphorus were subjected to a modification of the dextrose tolerance test followed by an injection of epinephrine. Blood sugar curves following these procedures and determinations of the hepatic glycogen before and after the modified dextrose tolerance test were made.

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16 Davis, N. C., and Whipple, G. H. The Influence of Fasting and Various Diets on the Liver Injury Effected by Chloroform Anesthesia, *Arch. Int. Med.* **23**: 612 (May) 1919.

The first functional deficiency of the liver to appear was a failure on the part of this organ to maintain the normal blood sugar level. Later, a progressive decrease in sugar tolerance was manifested which could be explained at least in part by lack of glycogen deposition in the liver following the administration of dextrose, water and insulin. In the last stages of poisoning after the modified dextrose tolerance test blood sugar curves ending in hypoglycemia were typical.

Epinephrine hyperglycemia in these animals was at first increased, then decreased, and finally abolished altogether. Thus the observed hypoglycemia is explained by failure of glycogenolysis to check the downward course of the blood sugar initiated by the stimulus of the ingestion of dextrose. An important additional factor probably is the compensatory rôle that the pancreas and the muscles play in the disposal of carbohydrates in case of hepatic insufficiency.

Even in late stages of phosphorus poisoning, the liver was found capable of transforming lactic acid into dextrose.

The experiments with acute phosphorus poisoning gave results very similar to those of chronic phosphorus poisoning.



# SOLAR RADIATION IN RELATION TO ENDEMIC GOITER

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## I THE RELATION OF SOLAR RADIATION TO THE DISTRIBUTION AND PREVALENCE OF ENDEMIC GOITER IN THE UNITED STATES

In the preparation of another paper<sup>1</sup> dealing with pellagra, in which the relative deficiency of solar rays in winter seemed to have a conditioned relationship to the distribution of pellagra, it was noted that the pellagra area in the United States, broadly speaking, ends where the area of endemic goiter begins, and that deficiency of winter sunshine is more marked in the goiter area than in the pellagra area. A somewhat similar relationship in the geographical distribution of the two diseases may be seen also in Europe and Asia. Southwest Virginia appears to be one of few areas of the earth's surface where endemic goiter and endemic pellagra meet on common ground, and in this area the prevalence of each is only moderate. This section deals with the correlation of deficiency in solar radiation and presence of endemic goiter, and seeks to present from the literature certain data suggestive of mechanisms possibly relating the two.

Probably no one now questions the influence of iodine in the prevention of simple goiter. It is important to bear in mind, however, that the physiologic action of any substance necessary for the organism is a matter of its availability for tissue needs rather than any mere question of supply. Iodine supply must, therefore, be considered in the light of its absorption from the intestinal tract (or by other routes) as influenced by factors such as the  $p_H$  of the intestinal tract, the possibility of its premature excretion after absorption (excretion as opposed to physiologic waste), its fixation with other substances that may render it unavailable for physiologic use (as with unsaturated fatty acids), its bound or unbound state, its diffusibility through membranes, the proportion in a state of ionization, the available supply in proportion to other substances with which maintenance of physiologic equilibrium is impor-

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1 Smith, J H. The Influence of Solar Rays on Metabolism. With Special Reference to Sulphur and to Pellagra in Southern United States, Arch Int Med 48 907 (Nov) 1931

tant (as possibly calcium),<sup>2</sup> and the condition of special tissues such as the thyroid gland to use the available iodine for specific purposes such as the manufacture of thyroxine and the storage of colloid. Thus it is seen that the available iodine may vary from the ingested iodine.

Marine<sup>3</sup> held that while goiter is apparently always due to a deficiency of iodine in the thyroid gland, the deficiency may be primary or absolute on the one hand, and secondary or relative on the other hand. Of the causal factors that have been suggested, Marine considered that water, poverty, damp sunless habitations and especially diet are of general importance today. Water, food and, through food, poverty are recognized modes of iodine deficiency. It is with the other factor, damp, sunless habitations, that this article chiefly deals.<sup>4</sup>

The elusive quality of the relationship of iodine to the thyroid gland is fully attested in many places. McClendon,<sup>5</sup> in reviewing the iodine determinations of drinking water from the State of Utah made in his laboratory, found that there was not a very close relationship between iodine and freedom from goiter. The iodine content of the same water supply was found to vary at different times. The water supply of Stanford University varied considerably during different months. It

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2 D. Marine (Ann Int Med 4 423, 1930) referred to the physiologic action of glutathione and other substances important in the reduction-oxidation processes of the organism as having possible goitrogenic influence. Practically all experiments and observations relating to the etiology of goiter result in recognition of the fact of an unexplained susceptibility in certain persons, leading the observer to postulate a "constitutional factor" (Webster, B., and Chesney, A. M. Am J Path 6 275, 1930). The feature of inheritance has been emphasized time and again, but comparatively little attention has been paid to the effect on inheritance produced by an early change of environment.

3 Marine, D. Studies on the Etiology of Goiter, Including Graves' Disease, Ann Int Med 4 423, 1930.

4 "Bad hygiene" has been considered a cause of goiter. McCarrison (McCarrison, B., and Newcomb, C. Indian J M Research 17 1061, 1930), defining this vague term for rats as "dirty cages," concluded that unhygienic conditions of life could cause simple hypertrophic goiter in these experimental animals. Since the control "clean cages" were submerged at intervals in boiling water, involving transfer of the animals, it would appear that environmental factors other than the condition of the cages might have to be evaluated. Excreta of rats are not always harmful to other rats, and in some circumstances may be actually beneficial. Nelson and Steenbock (quoted by Laurens, H. Physiol Rev 8 57, 1928), showed conclusively that when irradiated and nonirradiated rats are kept in the same cage, the stimulation to growth exerted on the nonirradiated rats is mediated by their consuming the antirachitically activated excreta of the irradiated animals. Webster and Chesney (Am J Path 6 275, 1930) found that there was no greater tendency to thyroid hyperplasia when rabbits were kept under conditions permitting easy contamination of food than when they were maintained in special cages under the best possible conditions.

5 McClendon, J. F. Iodine and Goiter in Utah and Use of the Cottrell Precipitator in Iodine Analysis, Proc Soc Exper Biol & Med 23 494, 1926.

does not seem that any adequate investigation has been made of the possibility that solar irradiation may be one influence in these variations and in the features of goiter epidemiology noted in the following paragraph

Numerous authors have cited examples of rivers and streams which, although "goitrigenous" at their source, lose this property during their course, and vice versa<sup>6</sup> Following a change of the source of water supply of towns and cities in the United States, the new supply coming from neighboring mountains (Oregon and Washington,<sup>7</sup> St George, Utah<sup>8</sup>), in some instances in which the water supply is piped from mountain springs (Lewistown, Mont<sup>9</sup>), a relatively high incidence of goiter is reported In Utah, Middleton<sup>8</sup> described the earlier source of supply as wells and water from surface springs In Virgin Valley, Utah (without reference to the source of the water supply), Middleton found a very high incidence of goiter and encountered enormous thyroid growths in the isolated mountain gorges In Montana, Foard<sup>9</sup> found that similar conditions—proximity to mountains, isolation, well and surface spring water—were associated with goiter endemicity second in degree only to the piped water supply from a mountain spring supplying Lewistown In connection with several reported epidemics of goiter, notation was made of an unusually cloudy, rainy or stormy season<sup>10</sup>

Consideration will now be given to certain data suggesting that iodine metabolism and the size of the thyroid gland may be influenced by irradiation of water, food or the skin of the animal organism, and that such an influence may be exerted either directly or through the well established power of ultraviolet irradiation to alter calcium metabolism

Hess and Lundagen<sup>11</sup> demonstrated a seasonal variation in the level of the inorganic phosphate of the blood of normal infants which corresponds to and is determined by the seasonal variation in the richness of the solar spectrum in ultraviolet rays Tisdall and Brown<sup>12</sup> showed an increase in bone ash from ultraviolet irradiation of rats on a rachitogenic diet Increased  $p_H$  of the intestinal contents tends to inhibit the absorption of calcium, and under these conditions ultraviolet irra-

6 Crotti, A Thyroid and Thymus, ed 2, Philadelphia, Lea & Febiger, 1922, p 269

7 Olesen, R Endemic Goiter in Oregon, Pub Health Rep **42** 2831, 1927

8 Middleton, G W Goiter in the Intermountain Region of Utah, J A M A **84** 1172 (April 18) 1925

9 Foard, F T Thyroid Enlargement Among Montana School Children, Pub Health Rep **39** 2354 (Sept 12) 1924

10 Crotti, A Thyroid and Thymus, ed 2, Philadelphia, Lea & Febiger, 1922

11 Quoted by Laurens, H Physiol Rev **8** 57, 1928

12 Tisdall, F F, and Brown, A Relation of the Altitude of the Sun to Its Antirachitic Effect, J A M A **92** 860 (March 16) 1929

diation promotes absorption and retention of both calcium and phosphorus (Grayzel and Miller<sup>11</sup>) These rays may also convert a latent into an active tetany<sup>13</sup> These observations, bearing on rickets, are introduced for the purpose of emphasizing that the relationship between ultraviolet irradiation and calcium metabolism is not confined to rickets, and for the purpose of comparison with other data to be referred to later in which iodine appears to be a substitution factor for ultraviolet radiation in the growth and maintenance of the weight of animals

Laurens<sup>14</sup> found

an unexpected similarity between the effects of change from roomlight to darkness and vice versa, and the effects following irradiation There is in both a stimulation of endogenous nitrogen metabolism resulting in a decrease in the balance

Probably any deviation from the usual so far as radiant energy is concerned, acts as a stimulus which disturbs the metabolism of nitrogen, calcium and phosphorus The antirachitic factor (vitamin D, either absorbed from the intestinal tract or produced by irradiation of the skin) works not only in the retention of calcium in rickets but also in the adult in which rickets is never observed It represents specifically the organic agent which promotes normal calcium anabolism It may cure rickets, it may promote growth, or it may simply prevent excessive loss of lime from the body Irradiation revives a depressed function

Goldblatt and Soames<sup>11</sup> found that irradiation of rats on a rachitic diet had a positive influence in maintaining weight and growth Laurens and Sooy<sup>11</sup> got similar results in albino rats on a normal diet Hanzlik, Talbot and Gibson<sup>15</sup> found that the administration of iodide had an effect similar to that just described for irradiation in maintaining the weight and growth of rats both on complete dietary and on a rachitic diet

Independent of any known association with calcium metabolism, the goitrogenic effect of certain foods appears to be subject to seasonal variations possibly dependent on the solar irradiation of growing vegetables Following the report of Webster and Chesney<sup>16</sup> that cabbage appeared to have a goitrogenic effect in rabbits, Marine, Baumann and Cipra<sup>17</sup> further investigated the conditions of this result Among other

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13 Cantarow, A Calcium Metabolism and Calcium Therapy, Philadelphia, Lea & Febiger, 1931, footnote 11

14 Laurens, H The Physiological Effects of Radiation, *Physiol Rev* 8 57, 1928

15 Hanzlik, P J, Talbot, E P, and Gibson, E E Continued Administration of Iodide and Other Salts Comparative Effects on Weight and Growth of the Body, *Arch Int Med* 42 579 (Oct) 1928

16 Webster, B, and Chesney, A M Studies in the Etiology of Simple Goiter, *Am J Path* 6 275, 1930

17 Marine, D, Baumann, E J, and Cipra, A Studies on Simple Goiter Produced by Cabbage and Other Vegetables, *Proc Soc Exper Biol & Med* 26 822, 1929

modifying influences, they found that so-called summer cabbage had a much less marked goiter-producing tendency than cabbage grown in the late autumn, so-called winter cabbage. Cabbage and other Brassicae were found to have both a goitrogenic and an antigoitrogenic factor. Marine and his collaborators affirmed that the possibility that thyroid hyperplasia due to feeding cabbage is dependent on an absolute deficiency of iodine can be dismissed. Webster and Chesney<sup>16</sup> noted that rabbits brought into their laboratory in the late fall or winter developed goiter on a cabbage diet much more promptly than those brought in during the spring and summer. Similarly, some of the large goiters tended to decrease in size slightly during the spring and summer. Webster, Clawson and Chesney<sup>18</sup> found that in goitrous rabbits the average production of heat was 16.6 per cent lower than in "normal" rabbits, those with the largest goiters showed the greatest depression in metabolic rate, the rate was practically constant in individual goitrous animals over a period of one year, provided there was no great change in the size of the gland. There was, however, a tendency, as stated, for the glands to decrease in size during the spring and summer.

The direct effect of irradiation on iodine metabolism has been studied by Pincussen and Roman.<sup>19</sup> These investigators found that rabbits to which potassium iodide had been administered by mouth, when later exposed to high mountain sunshine at Davos, Switzerland, showed a greatly increased excretion of nitrogen. Further, accepting as established and as a basis for a series of experiments the fact that iodine water solution under the influence of light gives off iodine, they reported the following results. In white mice, by irradiation with the mercury quartz lamp, in both normal animals and animals into which injections of inorganic iodine had been made, the proportion of organic to inorganic iodine decreases, and there is an increase of dialyzable iodine at the expense of the organically bound iodine.<sup>20</sup>

The seasonal variations in the goitrogenic properties of cabbage and the influence of light on the ionization and diffusibility of iodine in water and animals are suggestive only as to the influence of light on the available iodine supply for the thyroid gland of the human population of a given area.

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18 Webster, B., Clawson, T. A., and Chesney, A. M. Endemic Goiter in Rabbits. II. Heat Production in Goitrous and Non-Goitrous Animals, *Bull. Johns Hopkins Hosp.* **43**: 278, 1928.

19 Pincussen, L., and Roman, W. Effect of Irradiation on Iodine and Bromine Fractions in Animal Organism, Particularly Following Administration of Salts of Iodine, *Biochem. Ztschr.* **216**: 336, 1929.

20 Clark (The Physiological Action of Light, *Physiol. Rev.* **2**: 277, 1922) has shown a similar result, an increase in diffusible calcium of serum irradiated in quartz test tubes.

There is evidence to suggest that an increased intake of calcium may result in an increased requirement of iodine. McCarrison,<sup>21</sup> in Southern India, at an altitude of 6,000 feet, found that the effect on the thyroid gland of pigeons and rats of the excessive ingestion of lime, for a period of eight and a half months (from October to June), was to cause in certain individuals an increase in size of the organ of approximately 50 per cent. This increase was due to the abnormal accumulation of colloid material in the vesicles of the gland. There was no associated hyperplasia of the organ. The undue accumulation of colloid was preventable by increasing the intake of iodine proportionately to the excessive ingestion of lime. McCarrison concluded that a balanced adjustment of lime and iodine in the diet would appear to be necessary for the normal storage and resorption of colloid material by the thyroid gland, and that this observation would appear to have a bearing on the pathogenesis of colloid goiter in man.

There are recorded<sup>10</sup> instances of goiter endemicity on one bank of a stream and its absence on the other, corresponding to limestone and its lack. Lobenhoffer<sup>22</sup> affirmed that the intrusion of small wedges of shelly limestone amidst other formations will invariably augment the intensity of the goiter endemic. But it is not possible to generalize with regard to the distribution of calcium and its relation to iodine. The earlier tendency to general statements in the literature with reference to the iodine content of water, soil and vegetables has been followed by the report of striking exceptions and contradictions, as at Provincetown, Cape Cod, Mass.,<sup>23</sup> Marshfield, Ore.,<sup>23</sup> Mt. Clemens, Mich.,<sup>24</sup> Utah,<sup>25</sup> and in the vegetables of South Carolina, where the iodine content of vegetables appears to increase with distance from the sea.<sup>26</sup>

The tendency of goiter areas to be limited to the geological formations of the last glacial deposits has often been emphasized. So far as goiter tends to be endemic in mountainous countries, the following quotation fixes also the relation of goiter territory to the glacial deposits referred to. The *Encyclopaedia Britannica* (fourteenth edition) speaks

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21 McCarrison, R. The Effects of the Excessive Ingestion of Lime on the Thyroid Gland and the Influence of Iodine in Counteracting Them, *Indian J. M. Research* **13** 817, 1925-1926.

22 Quoted by Crotti (footnote 10).

23 Olesen, R. Endemic Goiter Among School Children, *Pub. Health Rep.* **42** 3180 (Dec. 30) 1927.

24 Olin, R. M. Iodin Deficiency and Prevalence of Simple Goiter in Michigan, *J. A. M. A.* **82** 1328 (April 26) 1924.

25 McClendon, J. F. The Distribution of Iodine with Special Reference to Goiter, *Physiol. Rev.* **7** 189, 1927.

26 Weston, W., and Remington, R. E. The South Carolina Food Research Commission. Preliminary Report on Its Organization and Activities, *J. A. M. A.* **92** 2161 (June 29) 1929.

of "the great extension of glaciers in almost every mountain center of the world in recent geological time" In more detail, endemic goiter territory tends to extend down mountain slopes into valleys and moraines and out on to plateaux at the base of mountains to conform to glacial movements Further, in certain instances in which goiter occurs conspicuously in nonmountainous countries, as around the Great Lakes and in the St Lawrence Valley of North America, still the goiter area overlies the more recent glacial deposits The significance of this correlation has never been established in terms of chemistry There is considerable evidence that the areas described are areas of low iodine content of soil and water, but there are many exceptions among the reported analyses Indeed, it is not certain that deficiency in iodine is a more constant characteristic than high calcium content of the soil and water in the area of glacial deposits so far as the references consulted show For the present it would seem more likely that the ultimate understanding of the etiology of goiter will explain its occurrence in the regions of glacial deposits rather than that the overlying of the two areas will explain the etiology of goiter

If it is tentatively assumed that lack of sunshine in winter is a contributing factor to goiter endemicity, it is not difficult to show how this factor may be intensified in several ways, the total intensity applying inclusively though somewhat variably to water, home grown food and the organism directly

The decreased angle of incidence of the sun's rays on the earth's surface in winter is a matter of common knowledge, and the decrease varies directly with proximity to the Arctic Circle However, the air mass penetrated by the sun's rays does not vary directly with latitude, but is greatly exaggerated by proximity to the Arctic Circle<sup>1</sup> Moreover, the days are short

Water vapor has a measurable influence on the depletion of ultra-violet wavelengths and on the total radiation in solar rays<sup>27</sup>

The decreased winter temperatures and snows of northerly latitudes tend to close housing, especially of the female population, accentuated by isolated living conditions

The topography of the country has a relation to solar radiation also Though the intensity of ultraviolet radiation may be increased at high altitudes, and though weather observation stations may record a high percentage of the possible sunshine, neither takes into account the deprivation involved in a rugged terrain The observations of weather bureau stations are, therefore, a better index of the solar irradiation of

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27 Kimball, H H The Distribution of Energy in the Visible Spectrum of Sunlight, Skylight and the Total Daylight, International Commission on Illumination, September, 1928

flat countries than of the much shadowed surface area of mountainous countries. Undoubtedly, if the observation is valid, the implication is that goiter is more frequent on the shaded slopes of mountains in a manner comparable to the woodsman's guides as to the points of the compass. While there are frequent references to goiter in valleys and

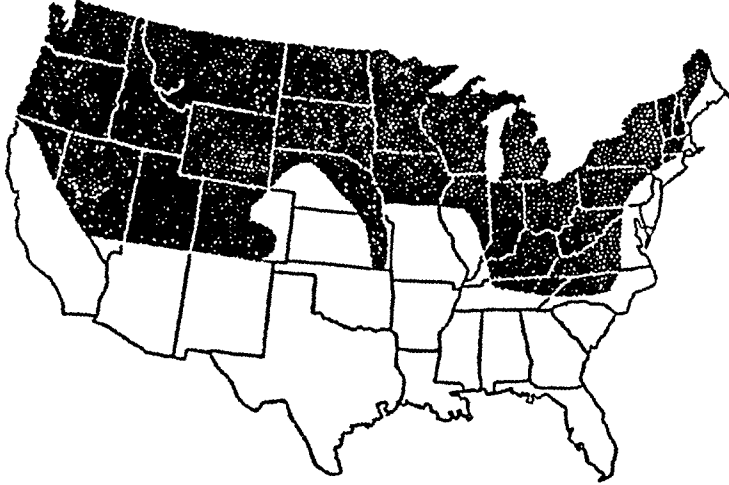


Chart 1—The iodine in drinking water in the United States. In the black area, waters contain from 1 to 22 parts of iodine per hundred billion parts of water, in the white area, from 23 to 18,470 parts. (After McClendon, J. F., and Hathaway, J. C. Inverse Relation Between Iodine in Food and Drink and Goiter Simple and Exophthalmic, *J. A. M. A.* 82:1668 [May 24] 1924.)

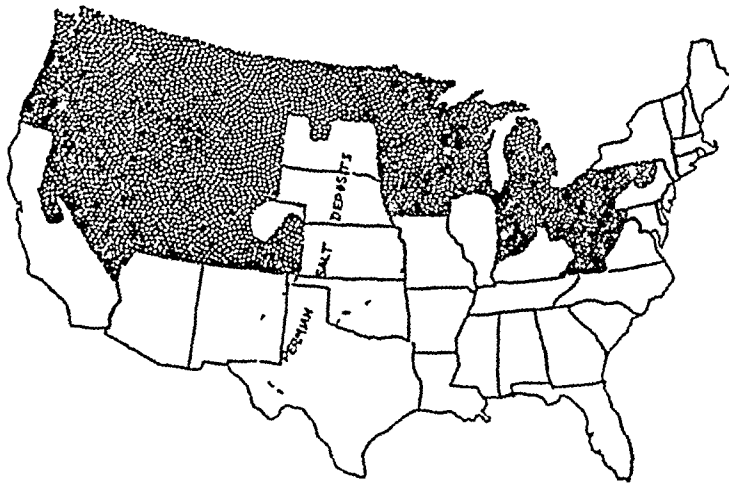


Chart 2—Simple goiter in the United States, from data of the Draft Board. In the white area, there were from 0 to 5 military goiters per thousand drafted men, in the black area, from 5 to 111. (After McClendon and Hathaway.)

mountain goiges, no recorded observation for or against its association with shaded slopes has been noted. The prevalence of goiter in mountainous countries, even in the tropics, is generally accepted, but it is difficult to appraise the comparative influence of climatic and geological factors with their implied chemical, and possibly other, significance.



Charts 1 and 2, respectively, reproduce McClendon and Hathaway's maps of iodine in drinking water in the United States and simple goiter in the United States from data of the Draft Board. Chart 3 illustrates the distribution of iodine according to McClendon's figures<sup>25</sup> and tends to confirm the observation of McClendon<sup>5</sup> that there is not a very close relationship between iodine and freedom from goiter.

Chart 4 illustrates the fact that endemic goiter is hardly a problem in states below latitude  $37^{\circ} 30' N$ . In the northwest the correlation

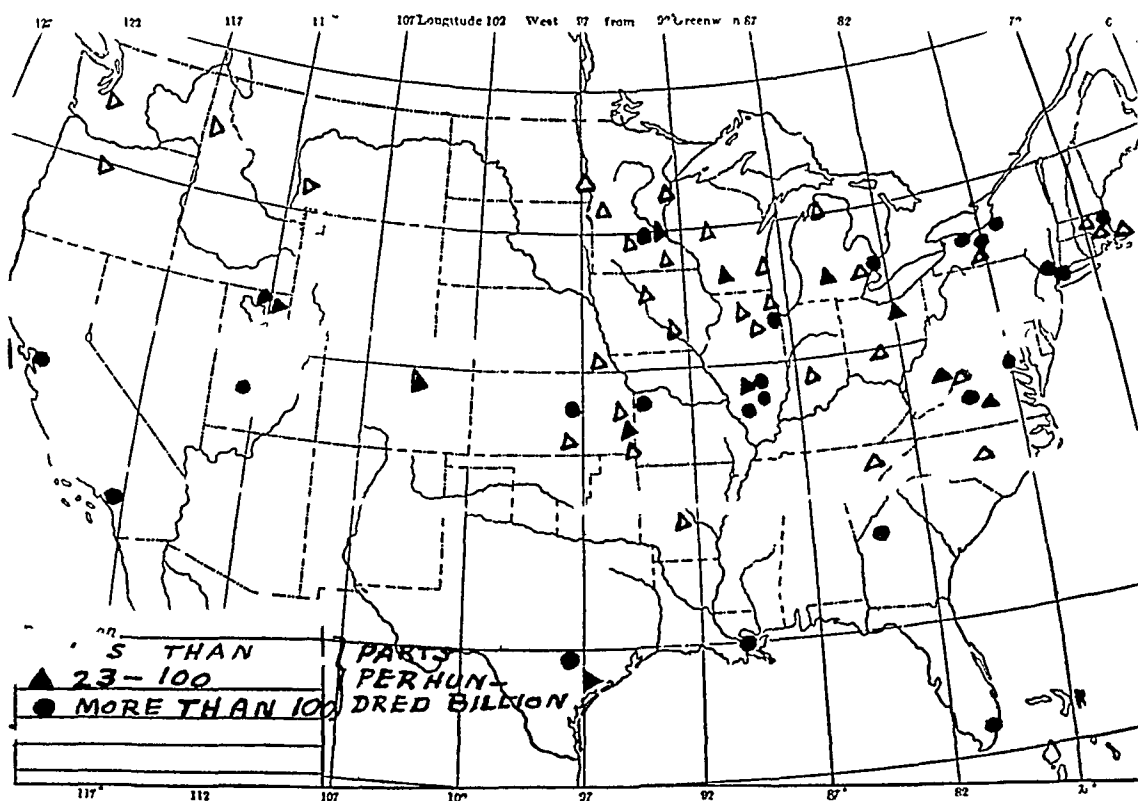


Chart 3—Iodine in the drinking water in the United States (After McClendon, footnote 25)

between goiter endemicity according to the data of the Draft Board and lack of winter sunshine is fairly close. If the figures for school girls reported in special surveys are considered, goiter is more prevalent in the area about the Great Lakes than in the Pacific Northwest, and the greatest prevalence corresponds in both areas quite closely to the greatest deficiency in winter sunshine. This correlation between goiter prevalence and lack of sunshine appears to be fairly close for the United States generally north of about 37 degrees latitude. The observation would appear to have a possible bearing on the etiology of goiter and on the low iodine content of the thyroid gland in the early spring as reported

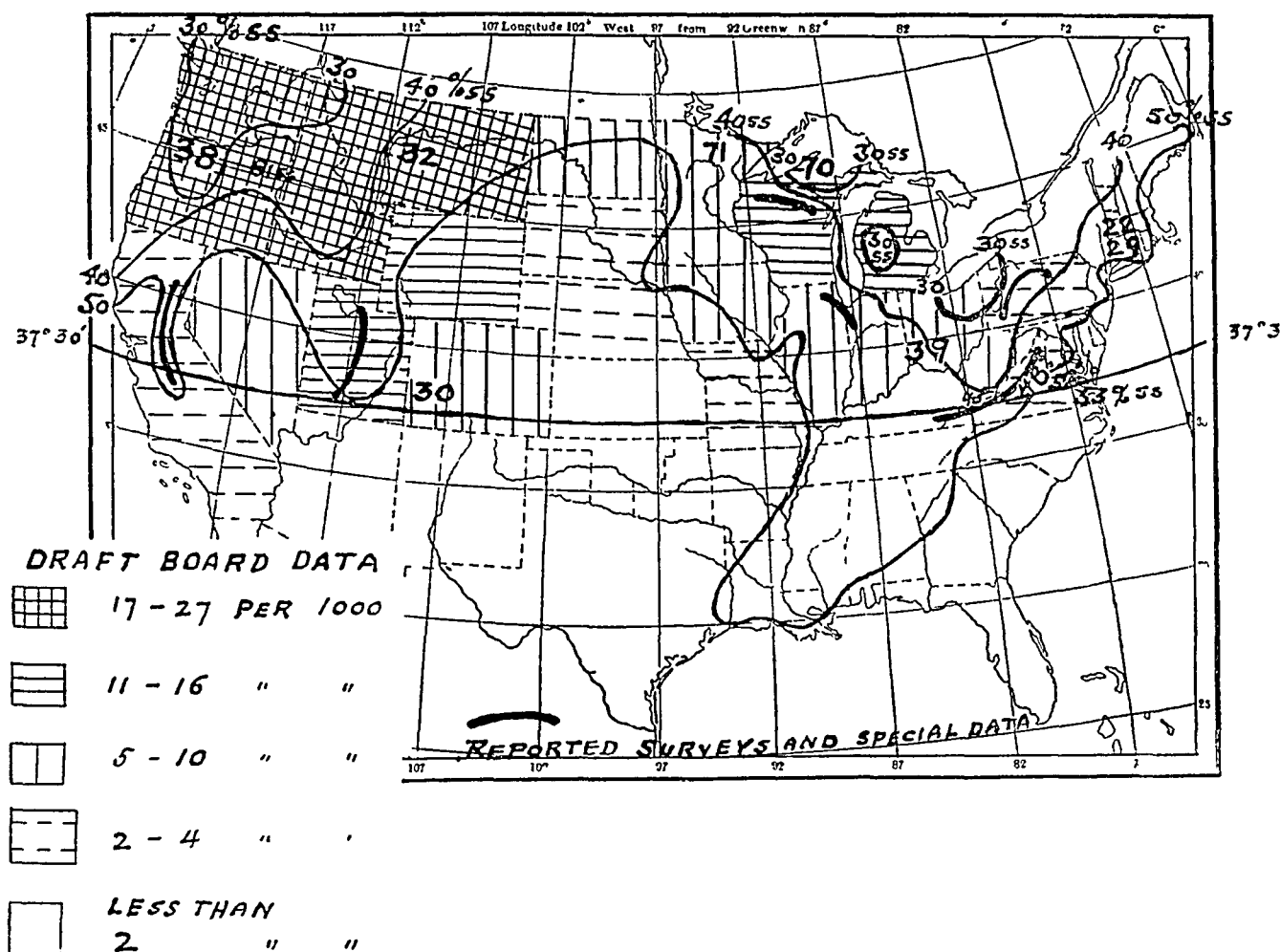


Chart 4—Hatching values are shown in the chart. The curves, as for 30%SS, indicate that the areas enclosed receive for the months of December, January and February an average of less than the indicated percentage of the possible sunshine according to data in Bulletin W of the United States Weather Bureau, covering the observation periods from the establishment of the stations to 1920, inclusive. The figures, as 53%SS, within the State of Virginia are intended to show a percentage of the possible sunshine of 53 per cent for the coastal area, 52 per cent, tidewater, 48 per cent, Piedmont, and 45 per cent, mountain area. Other figures inserted within the boundaries of states represent the highest percentage of goiter found in school girls in any area of the state included in special surveys, and with the exception of the figure 39 for Cincinnati, the location of the figure within the state boundary indicates the area of greatest prevalence observed within the state. The heavy black inserts also have the same significance as to the relative prevalence within the state. The sources of these data are as follows: Oregon (Cascade Mountains), Olesen (Pub Health Rep 42 2831, 1927), Montana (Rocky Mountains), Foard (Pub Health Rep 39 2354, 1924), Colorado (Rocky Mountains), Public Health Report 40 1, 1925, Minnesota, Olesen and Clark (Pub Health Rep 39 2561, 1924), Michigan, Olin (J A M A 82 1328, 1924), Cincinnati, Olesen (Pub Health Rep 39 1777, 1924), Connecticut, Olesen and Taylor (Pub Health Rep 41 1685, 1926), Massachusetts, Olesen and Taylor (Pub Health Rep 42 804, 1927), California (Sierra Nevada Mountains), Illinois, and Pennsylvania (Appalachian Mountains), McClendon and Hathaway's map (chart 2), Utah (Rocky Mountains), McClendon (Physiol Rev 7 189, 1927), Wisconsin, Olin, Virginia (Appalachian Mountains), information common to physicians in the state.

by Seidell and Fenger,<sup>28</sup> attributed fundamentally to temperature and weather conditions, and on the reported observations of the greatest incidence of simple goiter at the end of the winter season in some countries and at the end of the rainy season in certain tropical and subtropical countries

### CONCLUSIONS

Reported experimental evidence suggests that a lack of solar radiation may result in a deficiency of the iodine content of the thyroid gland through deficient irradiation of air, soil, food, drinking water or the skin of the organism, and that the mechanism may be a lack of diffusible iodine, an increase in a goitrogenic factor of certain vegetables or a disturbed calcium metabolism

The relation of solar radiation to the distribution and prevalence of endemic goiter in the United States is suggestive of a relationship of cause and effect which, in the light of present data, would be considered to mean that there tends to result from a deficiency of solar radiation a deficiency of iodine in the thyroid gland due to a lack of solar irradiation of air, soil, food, drinking water or the skin of the animal organism, tending to an increased prevalence of endemic goiter

## II THE RELATION OF SOLAR RADIATION TO THE DISTRIBUTION AND PREVALENCE OF ENDEMIC GOITER IN INDIA

In section I, dealing with the same subject as applied to the United States, the evidence was believed to suggest that a deficiency of solar radiation tends to result in an increased prevalence of goiter

In making a similar comparison for India, the data found to be available for arriving at an index of the distribution of solar radiation differ from those used for the United States. In the United States the relative deficit of solar radiation was determined from the weather bureau reports of the percentage of possible sunshine observed during the winter months. For India the monthly and annual precipitations at different stations have been used in connection with the latitude of the stations. The figures so derived have been compared with computations by Kimball of the depletion of solar rays by water vapor at varying angles of incidence of the sun's rays on the earth's surface. This comparison yields an index of the distribution of solar radiation in India.

Kimball's<sup>27</sup> figures for wavelengths below 346 millimicrons are shown plotted in chart 5. The interpolations are recognized to be liable to considerable error.

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<sup>28</sup> Seidell, A., and Fenger, F. Seasonal Variation in the Iodine Content of the Thyroid Gland, *J. Biol. Chem.* **13** 517, 1913

TABLE 1—Data for Weather Bureau Stations in India for Calculating an Index of Solar Radiation\*

No	Station Name	Latitude N		Longitude E	
		Degrees	Minutes	Degrees	Minutes
1	Ahmadabad	23	2	72	38
2	Akyab	20	7	92	57
3	Allahabad	25	28	81	54
4	Bangalore	12	58	77	37
5	Belgaum	15	52	74	39
6	Bombay (Colaba)	18	55	72	54
7	Calcutta (Alipore)	22	32	88	24
8	Cherrapunji	25	16	91	46
9	Cochin	9	58	76	17
10	Gauhati	26	11	91	48
11	Hyderabad	23	23	68	24
12	Jaipur	26	55	75	52
13	Kalat	28	58	66	28
14	Karachi	24	51	67	4
15	Kodaikanal	10	13	77	32
16	Lahore	31	34	74	21
17	Leh	34	10	77	40
18	Madras	13	4	80	17
19	Mandalay	21	59	96	8
20	Mangalore	12	52	74	53
21	Masulipatnam	16	9	81	12
22	Mergui	12	27	98	35
23	Moulmein	16	30	96	38
24	Nagpur	21	9	79	9
25	Patna	25	40	85	15
26	Peshawar	34	2	71	37
27	Port Blair	11	41	92	45
28	Quetta	30	12	67	00
29	Rangoon	16	47	96	13
30	Shillong	25	34	91	56
31	Simla	31	6	77	13
32	Waltair (Vizagapatnam)	17	42	83	19

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
9	9	76	9	June	27	April, Aug	0	0	0	0	114	1 48	52	57	33	0 87	19	10
15	10	77	7,689	Oct	9	April, Aug	2	16	0	16	62	1 41	59	56	34	0 99	7	8
27	11	92	59	June	18	April, Aug	0	0	0	0	115	1 515	49	55	35	0 82	24	11
4	12	77	3,021	Sept	6	April, Aug	1	8	0	8	35	1 505	50	54	36	1 06	0	0
20	12	74	72	June	38	April, Aug	0	0	0	0	128	1 442	56	54	36	0 77	29	17
22	12	98	66	July	31	April, Aug	0	0	0	0	162	1 468	53	54	36	0 68	38	20
18	13	80	22	Nov	13	April, Aug	3	24	0	24	49	1 306	69	53	37	1 00	6	12
5	15	74	2,562	July	15	April, Aug	0	0	0	0	49	1 52	48	51	39	0 96	10	4
21	16	81	15	Oct	8	May, July	3	24	0	24	39	1 33	67	50	40	0 99	7	12
23	16	96	77	July	45	May, July	0	0	0	0	190	1 42	58	50	40	0 57	49	28
29	16	96	18	July	21	May, July	0	0	0	0	99	1 505	50	50	40	0 78	28	14
32	17	83	38	Oct	9	May, July	3	24	0	24	41	1 335	67	49	41	0 96	10	13
6	18	72	37	July	24	May, July	0	0	0	0	72	1 494	51	48	42	0 84	22	11
2	20	92	20	July	53	May, July	0	0	0	0	203	1 395	61	46	44	0 48	58	34
19	21	96	250	May	5	May, July	0	0	0	0	35	1 58	42	45	45	0 92	14	3
24	21	79	1,017	July	13	May, July	0	0	0	0	46	1 535	47	45	45	0 87	19	8
7	22	88	21	Aug	13	May, July	1	8	0	8	64	1 475	53	44	46	0 80	26	14
1	23	72	163	June	11	June	0	0	0	0	28	1 544	46	43	47	0 91	15	5
14	24	67	13	July	2	0	1	8	1	9	7	1 52	48	42	48	1 00	6	2†
25	25	85	183	Aug	11	0	2	16	2	18	45	1 386	61	41	49	0 82	24	17
3	25	81	309	July	12	0	1	8	2	10	38	1 458	54	41	49	0 84	22	13
8	25	91	4,309	July	107	0	1	8	2	10	456	1 16	84	41	49	0 12	94	64
11	25	68	96	July	2	0	1	8	2	10	7	1 51	49	41	49	0 97	9	4†
30	25	91	4,920	June	16	0	0	0	2	2	83	1 505	50	41	49	0 69	37	18
10	26	91	196	July	12	0	1	8	3	11	66	1 44	56	40	50	0 73	33	19
12	26	75	1,431	July	8	0	1	8	3	11	23	1 46	54	40	50	0 88	18	11
13	28	66	6,630	Jan	1	0	5	40†	5	45	7	1 07	93	38	52	0 92	14	28†
28	30	67	5,502	March	1	0	3	24†	7	31	9	1 28	72	36	54	0 87	19	20†
16	31	74	702	July	6	0	1	8	8	16	20	1 42	58	35	55	0 80	26	17
31	31	77	7,232	July	21	0	1	8	8	16	79	1 355	65	35	55	0 58	48	31
17	34	77	11,503	Aug	1—	0	2	16†	11	27	3	1 334	67	32	58	0 82	24	20†
26	34	71	7,137	March	2	0	3	24	11	35	13	1 218	78	32	58	0 78	28	28

\* The columns as numbered indicate 1, station number, 2, station latitude, 3, station longitude, 4, station altitude in feet, 5, month of maximum precipitation, 6, precipitation in inches in the month of maximum precipitation, 7, months in which sun is at zenith, 8, months elapsing between last month in which sun is at 90 degrees and month of maximum precipitation, 9, values in column 8 multiplied by 8, the approximate number of degrees per month traveled by the sun (47 degrees in six months), 10, latitudinal distance above 23 degrees 30 minutes, 11, values in column 9 plus values in column 10, giving degrees of declination of the sun from the zenith in the month of maximum precipitation, 12, annual precipitation in inches, 13, index of intensity of solar radiation obtained by plotting columns 6 and \*11 into chart 5, 14, index of intensity of solar radiation subtracted from 2 to give an inverse index of solar intensity, 15, minimum angle of the sun (December), 16, sun distant from the zenith in December, 17, index of intensity of solar radiation obtained by plotting columns 12 (annual precipitation in inches) and 16 into chart 5, 18, index of intensity of solar radiation (column 17) subtracted from 106 (maximum index) to give an inverse index of duration or extent of solar intensity, 19, column 14 plus column 18 divided by 2 to give mean of the two methods, precipitation in month of maximum precipitation and degrees of sun's declination from zenith in month of maximum precipitation, and annual precipitation and sun's declination from zenith in December, respectively minus 25 (minimum index thus obtained) to give zero as minimum index.

† As the angle of declination of the sun is great in the month of maximum precipitation, with only slight precipitation (less than 10 inches per annum), an exaggerated value is doubt less given to the value in column 14, and thus to the value in column 19.

‡ Annual precipitation less than 10 inches.

Table 1 shows certain data reported from weather bureau stations in India,<sup>29</sup> the annual and monthly precipitation for each station, the angle of the sun's rays at each station in the month of maximum precipitation and in December, the angle being measured in terms of degrees distant from the zenith. These data as to the angle of the sun's rays and precipitation, plotted into chart 5, afford a numerical index of solar radiation according to Kimball's computations<sup>30</sup>. The comparison furnishes an index only rather than a measurement, as precipitation in inches is substituted for Kimball's value of water vapor per centimeter. In the last column of table 1, the index is transcribed into a

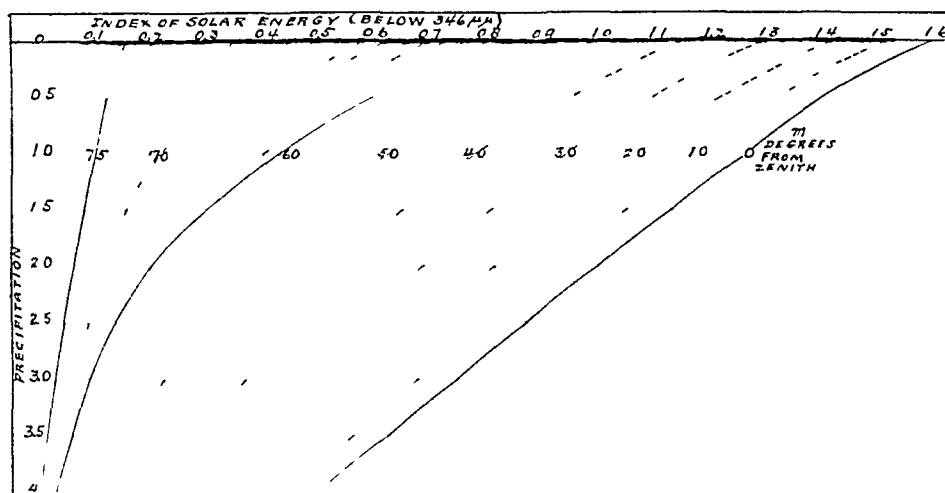


Chart 5—Energy distribution in solar rays below  $346\mu\mu$ , as modified by air mass and water vapor.  $m$  represents air mass,  $m$  equal to 0, solar energy outside the atmosphere,  $m$  equal to 0.764, for Calama, Chile, sun in zenith, atmospheric pressure averages 581 cm,  $m$  equal to 1, for Washington, D C, sun in zenith,  $m$  equal to 2, for Washington, D C, solar zenith distance, 60 degrees,  $m$  equal to 4, for Washington, D C, solar zenith distance, 75 degrees 7 minutes (After Kimball)

29 Clayton, H H. World Weather Records, Pub 2913, Washington, D C, Smithsonian Institution, 1927

30 It is not intended to assume a special influence for the wavelengths used from Kimball's table, though to the shorter lengths of solar radiation is generally ascribed a biologic influence greater than to the longer, wavelengths. The radiation index arrived at by plotting the declination from 90 degrees of the sun's angle in the month of maximum precipitation and the precipitation in this month is conceived of as an index of intensity of depletion of solar rays, whereas the radiation index arrived at by plotting the declination in December and the annual precipitation is conceived of as an index of duration or extent of depletion of solar rays. There is no certainty of the validity of either assumption. Probably the whole method of computing a radiation index is needlessly complex, and if simplified it would be to the advantage of clarity at least. Figures for cloudiness at the different stations, similar to those employed in the paper on conditions in the United States, might be useful if available. Precipitation is not an accurate index of either cloudiness or humidity.

reversed scale In this form the index is shown on the maps of distribution of goiter as prepared by McCarrison<sup>31</sup> (chart 6), and by Megaw<sup>32</sup> (chart 7), as also on the map of distribution of deaf-mutism as prepared by Stott and his co-workers<sup>33</sup> (chart 8) The last comparison has the advantage that deaf-mutism is noted in the census of India and

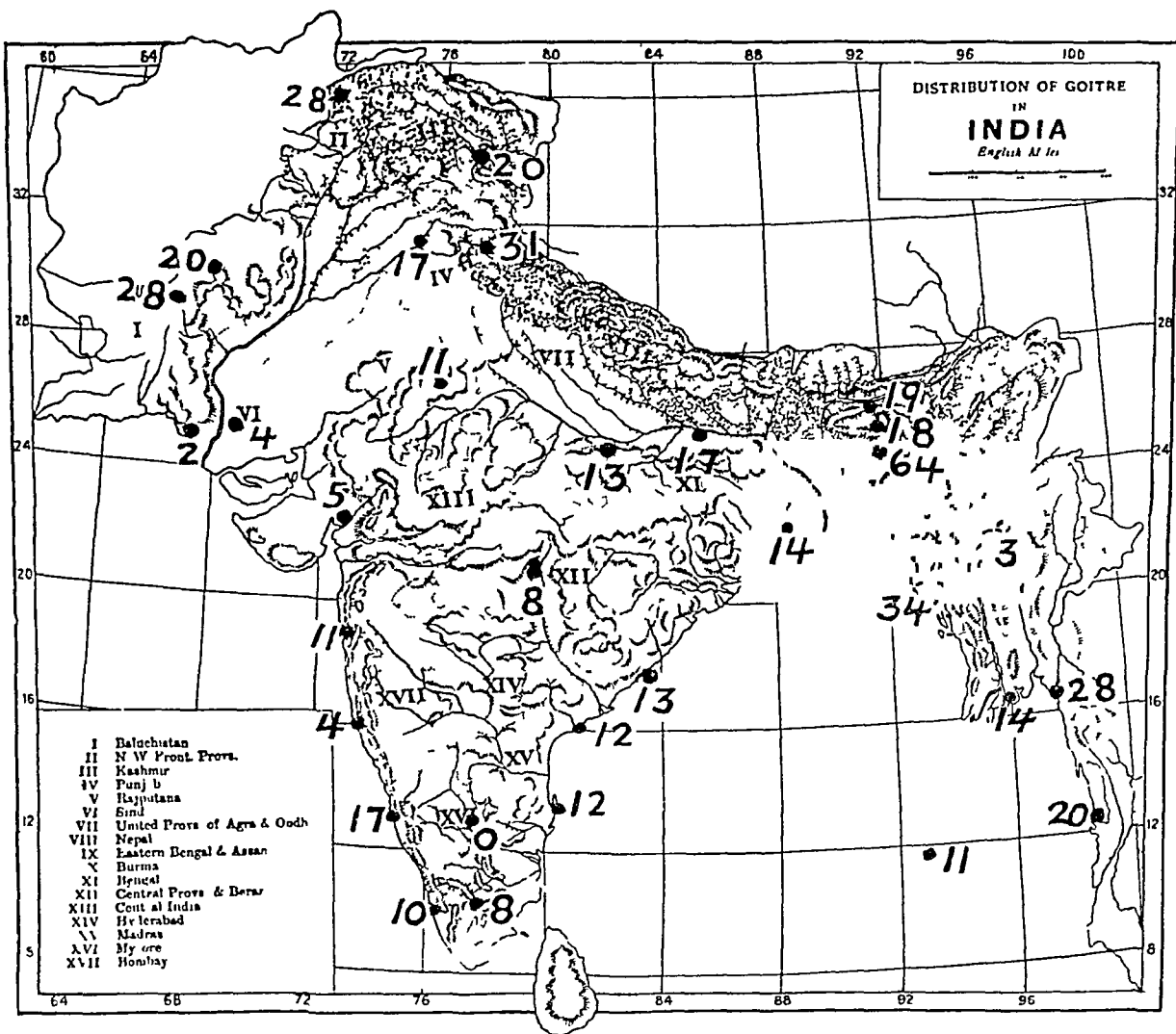


Chart 6—Distribution of goiter in India (after McCarrison) The numerals indicate the radiation index (depletion) at thirty-two weather bureau stations

the figures are given per unit of population, it has the disadvantage that it substitutes an index of goiter (deaf-mutism) for the disease

31 McCarrison, R The Distribution of Goitre in India, *Indian J M Research* 2 778, 1914-1915

32 Megaw, J W D, and Gupta, J C The Geographical Distribution of Some of the Diseases of India, *Indian M Gaz* 62 299, 1927

33 Stott, H, Bhatia, B B, Lal, R S, and Rai, K C The Distribution and Cause of Endemic Goiter in the United Provinces, *Indian J M Research* 18 1059 (April) 1931

itself The basis on which Stott and his co-workers claimed the validity of the substitution is as follows

The close connection between deaf-mutes, cretins and goiter is well known, but since the census records the distribution of deaf-mutes in each province of India, and since these figures are utilized later as an indication of the distribution of goiter in India, it is desirable to produce definite evidence of this close connection

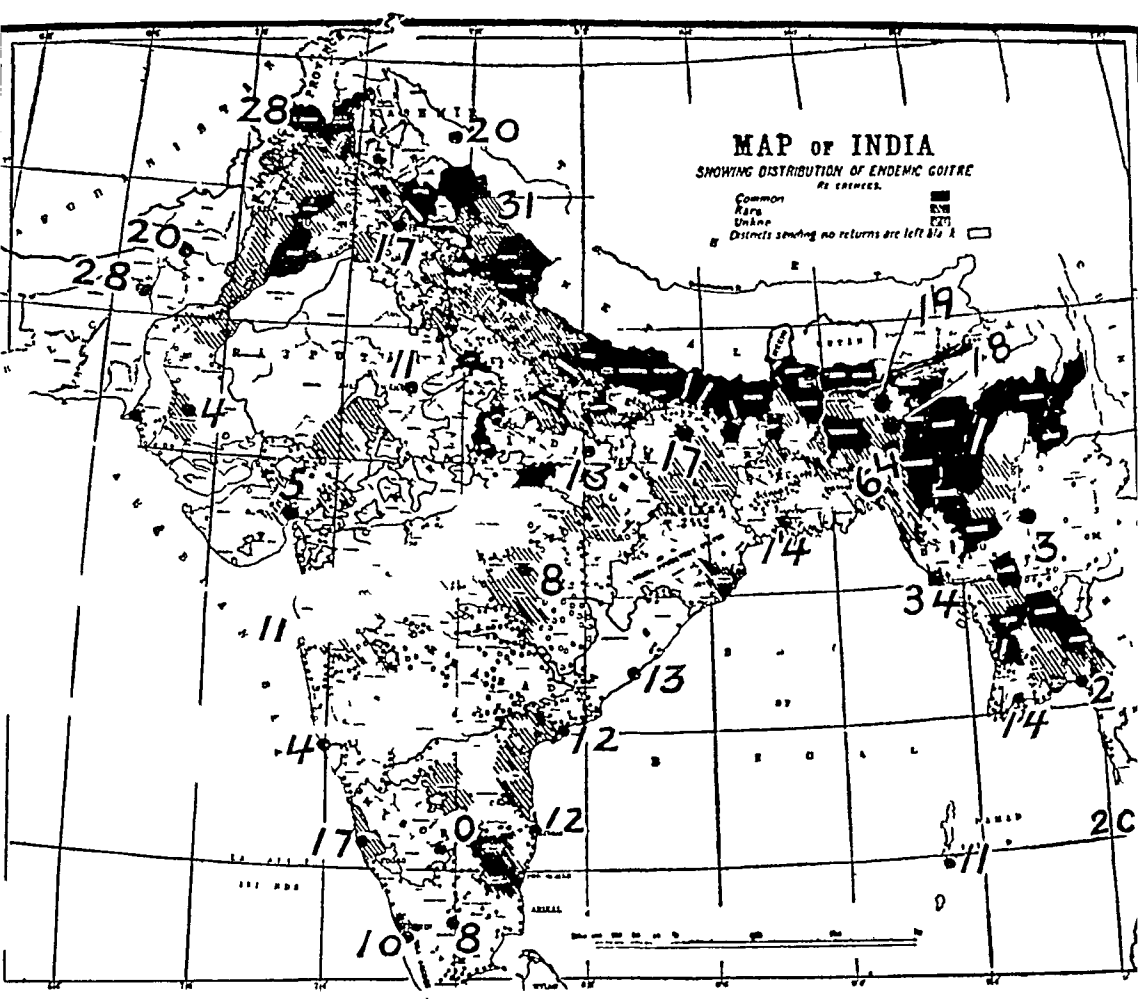


Chart 7—Distribution of endemic goiter in India (after Megaw and others)  
The shading indicates the presence of goiter black, common, hatched, rare, small circles, goiter unknown, blank spaces, districts sending no returns The numerals indicate the radiation index (depletion) at thirty-two weather bureau stations

In the United Province census report for 1901, the following figures are given for the Gonda Tahsils

Tahsil	Goiter Cases Attending Dispensaries			Deaf-mutes per 10,000
	Total Number	per 10,000 Population	or as	
1 Gonda	19,385	509	56	47
2 Tarabganj	29,971	821	91	93
3 Utraula	5,899	90	10	27

Allowing for the large percentage of non-goitrous Nepalese who come to the Utrula dispensary with ordinary complaints, the tahsil ratio for goiter and for deaf-mutes is practically identical. This is interesting evidence. But similar figures could be presented for any sufficiently endemic area in the U P, for goiter, cretinism and deaf-mutes everywhere occupy the same areas of the highest endemicity.

In India, therefore, the distribution of deaf-mutes may be taken as an index of the distribution of severely affected endemic goiter areas.

The correlations shown on the three maps (charts 6, 7 and 8) between the relative deficiency of solar radiation and the presence of

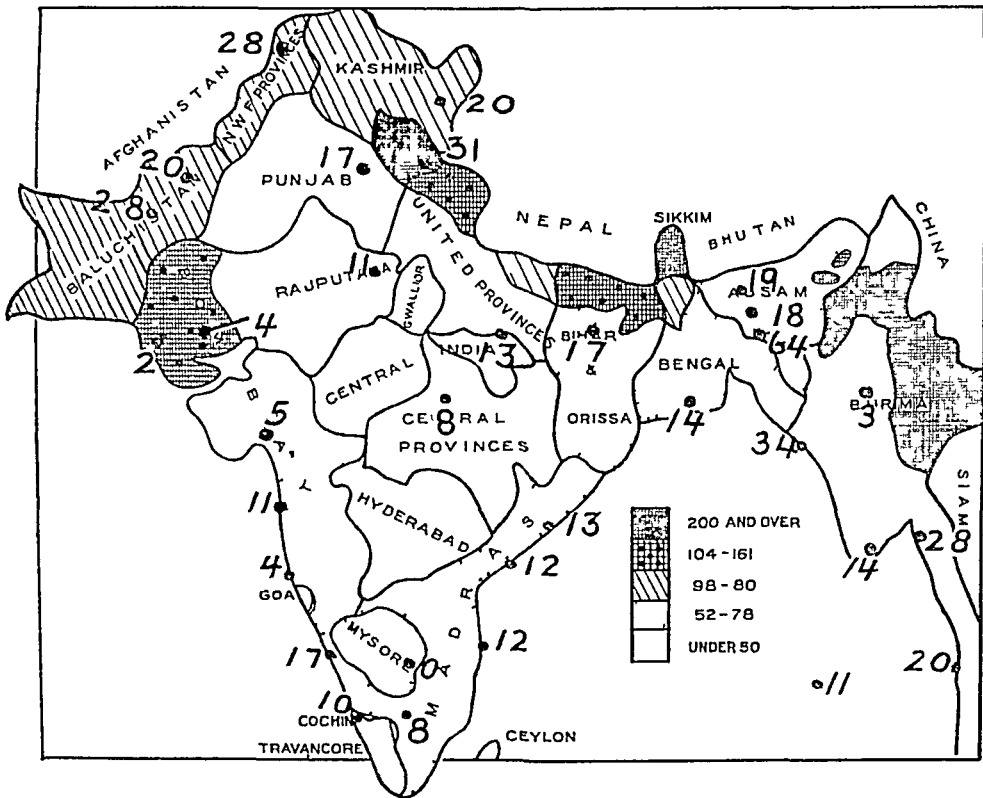


Chart 8—Distribution of deaf-mutes per hundred thousand population in India (after Stott and others). The significance of the shading is shown in the chart. The numerals indicate the radiation index (depletion) at thirty-two weather bureau stations.

goiter and deaf-mutism, respectively, appear to be fairly close except for the sub-Himalayan area along the northern border of India. The exception appears to be due to the fact that there are no reports of precipitation from any station located north of the Ganges River, where the prevalence of goiter is relatively great. That precipitation in this area is also great in comparison with the area south of the Ganges is shown by reference to charts 9 and 10. The area is at a relatively great distance from the equator, and is subject, therefore, to a relatively great depletion of solar radiation by air mass. In this connection the follow-



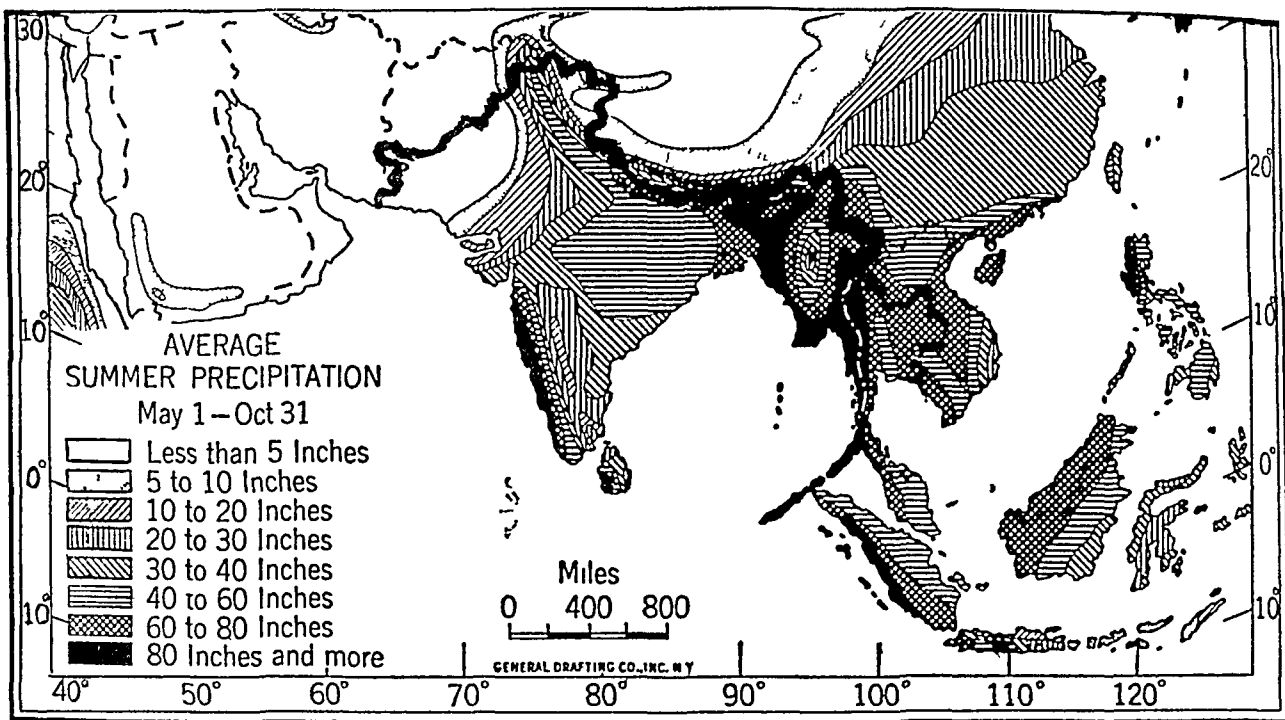


Chart 9—Average summer precipitation in India, from May 1 to October 31 (reproduced from Barrows, H H , Parker, E P, and Parker, M T Geography, Europe and Asia, New York, Silver, Burdett and Company, 1927, where the chart was reproduced from Philips' Modern School Atlas (by permission of Messrs George Philip and Son, Ltd, London) The borders of India drawn in black in the present reproduction are not to be confused with the black areas representing precipitation of 80 inches and more, as in Burma, where the boundary line appears in white

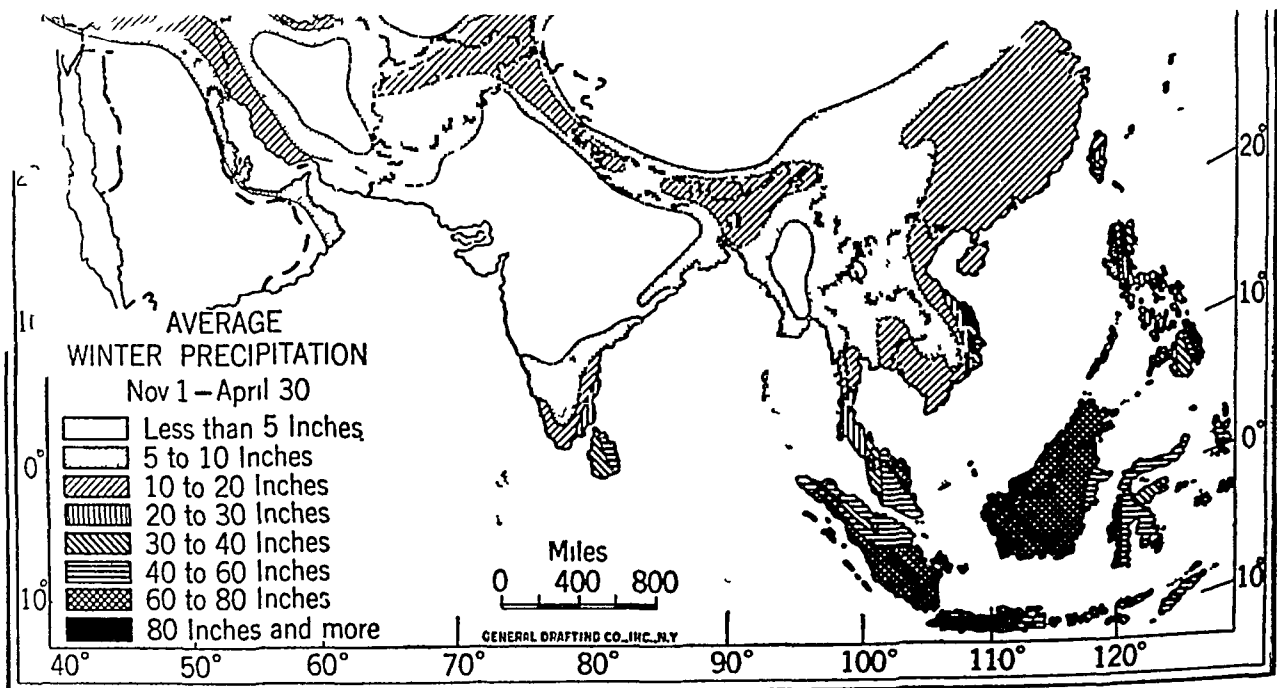


Chart 10—Average winter precipitation in India, from November 1 to April 30 (reproduced from the same sources as chart 9)

ing quotation from the *Encyclopaedia Britannica* (eleventh edition) appears to be significant

India flora—For the Malayan area, which Sir Joseph Hooker describes as forming “the bulk of the flora of the perennially humid regions of India, as of the whole Malayan peninsula, Upper Assam Valley, the Khasi mountains, the forests of the base of the Himalaya from the Bramaputra to Nepal, of the Malabar coast, and of Ceylon” indicative of the character of the climate of the sub-Himalayan area

The sub-Himalayan tract is, therefore, apparently subject to solar radiation of a degree comparable with that of Simla (latitude  $31^{\circ} 6'$ , longitude  $77^{\circ} 13'$ , radiation index 31)

The foregoing considerations appear to furnish suggestive evidence of a direct relation between a deficit of sunshine and the presence of endemic goiter in India similar to the broad scale study of the same correlation in the United States <sup>34</sup>

McCarrison's <sup>31</sup> discussion of distribution with respect to rainfall is as follows

Speaking generally there appears to be little connexion between the rainfall and the prevalence of goitre. The disease is as common in some parts of India where the rainfall is scanty as in others where it is very high. I have, however, received many reports in which it is stated that goitre most commonly commences and most rapidly develops during or after the rains. So constant is this belief, first recorded by Macnamara <sup>35</sup> thirty years ago, that I am inclined to attach considerable importance to it, and to attribute to “the rains” an etiological influence which depends rather upon factors associated with them—inundation, contamination of drinking water-supplies by surface washings, etc.—than upon the rainfall itself

The paper of Stott and his co-workers gives opportunity for more detailed comparison of climatic conditions and the distribution of goiter. These authors interpret their observations as pointing to the influence of lime in the causation of goiter, and in support of their thesis cite extensive evidence both general and specific. Their position may be represented by the following quotation from their summary

Where the local distribution of this disease group (congenital deaf-mutes, cretins and goitrous persons) has been investigated it is associated with a definite water-supply and in that water-supply lime is usually found present in excessive amounts

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34 It is of interest to note that the lowest radiation index, zero, is at Bangalore (latitude  $12^{\circ} 58' N$ , longitude  $77^{\circ} 37' E$ , altitude 3,021 feet), nearly the location of Coonoor (latitude  $11^{\circ} 21' N$ , longitude  $76^{\circ} 49' E$ , altitude about 6,000 feet [National Geographic Society]), where goiter is reported to be notable for its rarity. McCarrison (*Indian J. M. Research* **18** 1311, 1931) stated “It should here be emphasized that three conditions in Coonoor—altitude, calcium content of the soil and iodine content of the soil and vegetables grown upon it—all have an influence on the thyroid gland. The height of Coonoor above sea level is 6,000 ft, the soil is very poor in calcium, and relatively rich in iodine.”

35 Macnamara, F. N. *Climate and Medical Topography in Their Relation to the Disease-Distribution of the Himalayan and Sub-Himalayan Districts of British India*, London, Longman [and others], 1880

The interpretation by these authors of their several references to climate is perhaps indicated by the following quotation

South of the Gogra (river), in the dry sandy areas of Fyzabad, there is no goiter, because the Gogra tributaries which keep the soil moist and calcium-saturated all flow from the north

There appears to be no inherent conflict between the view of these authors and that of a more direct influence of deficiency of solar rays as affecting the air, soil, food, drinking water or the skin of the animal organism of the population concerned. Regardless of interpretation, it

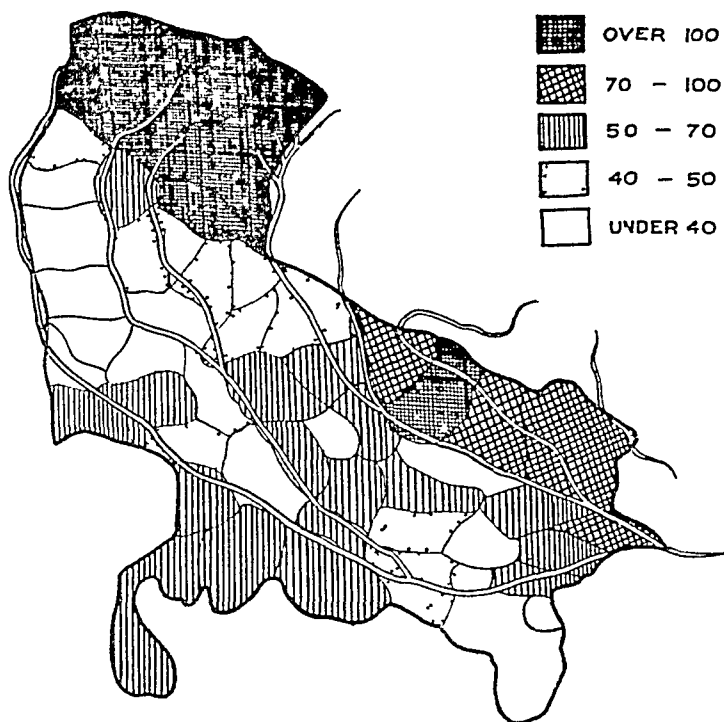


Chart 11—Distribution of deaf-mutes in the United Provinces of India, per hundred thousand males, Census, 1921 (After Stott and his co-workers)

seems pertinent to reproduce maps 5, 6 and 8 of Stott and his co-workers as charts 11, 12 and 13 of this series, together with certain extracts from the paper of these authors referring to climatic conditions

Charts 11 and 12, and especially chart 13, permit a comparison of the goiter-free area of Fyzabad and Barabanki with the heavily goitrous districts of Bahraich, Gonda, Basti and Gorakhpur just north of the Gogra River. The dry character of Fyzabad has been referred to. The sub-Himalayan tract of the United Provinces, lying just north of the Gogra, is shown with the distribution of goiter in chart 13, as also its division into three transversely parallel tracts. The characteristics of these three natural subdivisions as given by the authors quoted are as follows

- (1) The foothill (Terai) tract
- (2) The plateau (Uparhar) tract
- (3) The low-lying moist (Tarhar) tract

The latter is an endemic area of high degree. The former two areas will also be considered in this section.

The sub-mountainous foot-hill (Terai) tract lies between the Himalayas to the north and the river Rapti to the south. The area is full of small mullahs, dry in the hot weather but which serve to draw off mountain water in the rains and which then form many swamps. To the extreme north there is a line of forest



Chart 12—Key map to the districts and rivers of the United Provinces of India (After Stott and his co-workers)

land (as jungle is cleared and water supplies are improved the disease decreases) where the heavy clay forming the soil of this region gives way to sandy clay which is interspersed with water-worn limestone boulders and lime kanker from the mountains.

Along the Rapti river the villages are goitre free, nor does the disease become intense until about one mile from the forest border is reached, where the villages commence to show an increasing prevalence from 3-5 per cent. The worst villages, some of which show a rate of 30 per cent, are situated on the edge of the rivulets. The disease in general is not severe here.

The plateau (Uparhar) tract is separated from the foot-hill tract on the north by the river Rapti, and from the low-lying moist Tarhar tract to the south by the rivers Sarju, Tehri and Kuwano. The tract is a slightly raised plateau. The soil

is a stiff clay, unsuited to maize but the grain harvests are rich and the Uparhar is the most flourishing part of each district Wells are plentiful The tract is almost free from endemic goitre

In the low marshy (Tarhar) tract the climate is naturally humid the tract shows intensely endemic areas where the tributaries from the Himalayas join the Gogra The most endemic of all areas is that lying between the three rivers Tehri, Sarju and Gogra where the goitre rate is 70 per cent and which is known as "the home of fools" The soil of these areas is intensely damp and the subsoil water is at a high level, especially during the rains Like that of the Padrauma Tahsil the soil is alluvial, friable and porous with 9 per cent calcium

The climate is very moist, the rainfall (50-70 inches) being higher than in any other plain district of the province



Chart 13—The distribution of goiter in the Bahraich, Gonda, Basti and Gorakhpur districts of the United Provinces, India (After Stott and his co-workers) The shading indicates gray, 5 per cent, hatched, from 10 to 25 per cent, small dots, from 25 to 35 per cent, small circles, from 35 to 50 per cent, and black, from 50 to 70 per cent

In the Himalayan tract (of the United Provinces) unlike the plains where endemic goitre is found in large areas, in the hills goitre is scattered in different and often not adjacent villages These endemic villages are situated in the moist river valleys Villages over 5000 feet in cool climates appear free

In no waters, goitrous or otherwise in the U P was iodine noted

The foregoing references to the distribution of goiter could be supplemented by references to the distribution and prevalence of deaf-mutism in connection with climatic conditions involving the depletion of solar radiation The quotations that have been made appear to take on

special significance in view of the following observations by Stott and his collaborators

Season New goitres especially arise, old goitres enlarge and all goitres most rapidly develop during and after the rains, i e., during October, November and December For it is during the monsoon in the plain areas that the rivers overflow their banks and alluvium with the goitre producing substance in it is spread over the soil and readily reaches the shallow wells Attendance of out-patients at the various dispensaries for goitre increases largely during the months following the rains

Chart 14, reproduced from the paper of Stott and his co-workers, shows this tendency to increase in attendance at the dispensary of the

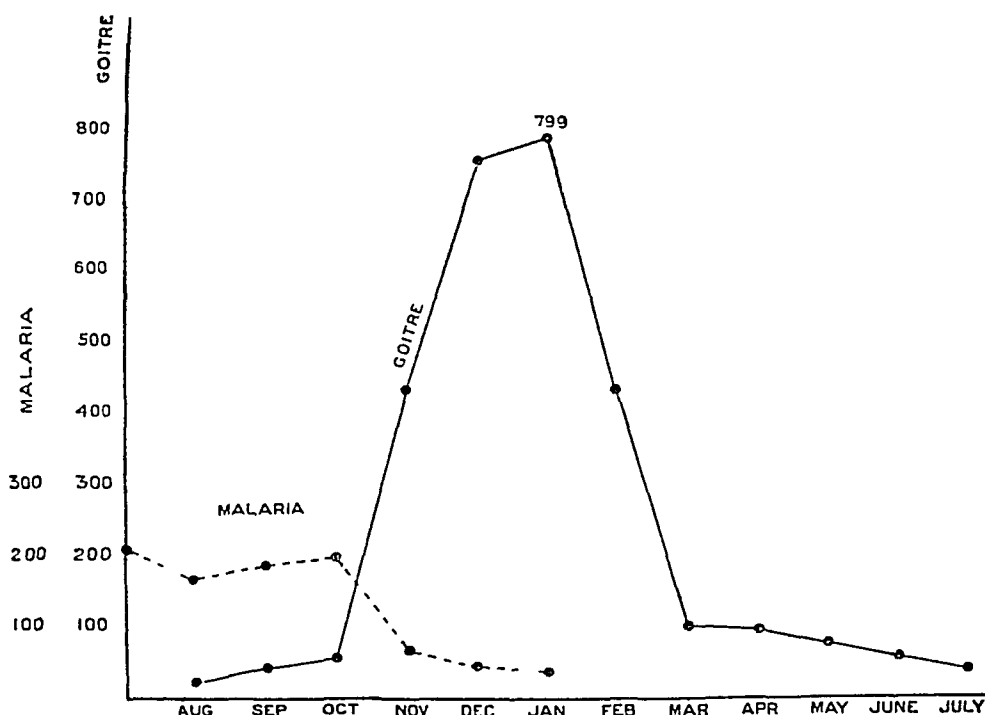


Chart 14—The monthly goiter (and malarial) attendance at the Banpur Hospital, 1925-1926 (After Stott and his co-workers)

Banpur Hospital (latitude  $19^{\circ} 47' N$ , longitude  $85^{\circ} 10' E$ <sup>36</sup>) in the months following the rains This location on the east coast is about midway between Calcutta on the north and east and Waltair on the south and west, and the monthly distribution of rainfall at these two stations is as follows<sup>29</sup>

Jan	Feb	March	April	May	June	July	Aug	Sept	Oct	Nov	Dec	Year
Calcutta												
0.42	0.99	1.38	2.18	5.56	11.91	12.70	13.38	10.01	4.90	0.65	0.24	64.32
Waltair												
0.36	0.48	0.33	0.71	2.31	4.56	4.68	5.75	7.21	9.36	4.10	1.21	41.05

<sup>36</sup> National Geographic Society, Washington D C, personal communication

## CONCLUSION

The data in this section appear to support the conclusions in the first section dealing with endemic goiter in the United States, namely, that a deficiency in solar radiation tends to a deficiency of the iodine content of the thyroid gland due to a lack of irradiation of the air, soil, food, drinking water or the skin of the animal organism, tending to an increased prevalence of endemic goiter

### III THE RELATION OF SOLAR RADIATION TO IODINE OF THE SOIL AND THE DISTRIBUTION AND PREVALENCE OF ENDEMIC GOITER IN NEW ZEALAND

In section I, dealing with the relation of solar radiation to the distribution and prevalence of endemic goiter in the United States, the evidence was believed to suggest that a deficiency of solar radiation tends to an increased prevalence of goiter

In section II, examination of the data for India seemed to point to the same conclusion. The index of solar radiation used in the two sections was different on account of differences in the data available. For the United States solar radiation was expressed in terms of percentage of possible sunshine, for India the index was the depletion of certain rays of the sun by water vapor at varying angles of incidence of the sun's rays on the earth's surface. The relative depletion at the different weather bureau stations in India was arrived at by taking into account the sun's angle and the precipitation. A scale of precipitation in inches was substituted for the measurement of water vapor in centimeters if all the water vapor of the air were precipitated, as described in Kimball's<sup>27</sup> article. With this substitution, an index of depletion of solar radiation was calculated by comparison with Kimball's standards.

In this section data reported by Hercus, Benson and Carter<sup>37</sup> permit a consideration of solar radiation in relation to iodine of the soil of New Zealand in addition to the relationship discussed in the two preceding sections. In this section the index of solar radiation is the same as that described for India with the following differences. The precipitation and the sun's angle during the month of lowest incidence of the sun's rays (June in New Zealand), compared with Kimball's standards, is used as the index of radiation. Since the actual monthly precipitation in June was not available for all the districts of New Zealand under consideration, this factor was estimated by taking the annual precipitation for the district as given in the article of Hercus, Benson and Carter and applying to this annual rainfall the relative

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37 Hercus, C. E., Benson, W. N., and Carter, C. L. Endemic Goitre in New Zealand, and Its Relation to the Soil-Iodine, *J. Hyg.* **24** 321, 1925

amount in June as suggested by the reported June precipitation at four weather bureau stations in New Zealand in "World Weather Records,"<sup>29</sup> assuming for each district in New Zealand a monthly distribution of rainfall corresponding to that at the nearest station for which the data

TABLE 2—*Data Relative to Solar Radiation of New Zealand Districts* \*

1	2	3	4	5	6	7	8
Degrees	Minutes	Degrees	Minutes	Degrees	Minutes		
1	47	19	30	70	30	H	60
2	46	30	20	70		H	45
3	46		20	69	30	H	40
4	46		20	69	30	C	35
5	45	30	21	69		C	22
6	45	30	21	69		C	22
7	46		20	69	30	C	37
8	45		21	68	30	C	20
9	44		22	67	30	C	70†
10	43	30	23	67		C	70†
11	43	30	23	67		C	40
12	43		23	66	30	C	70†
13	42		24	65	30	C	26
14	41	30	25	65		W	50
15	42		24	65	30	H	100
16	41	15	25	64	45	W	60
17	41	15	25	64	45	W	60
18	41		25	64	30	W	40
19	39	30	27	63		W	40
20	38	30	28	62		A	50
21	40	30	26	64		W	40
22	40	15	26	63	45	W	40
23	39	45	26	63	15	W	40
24	39		27	62	30	W	65
25	39	30	27	63		W	70
26	39		27	62	30	A	60
27	38	15	28	61	45	A	60
28	38		28	61	30	A	60
29	38	30	28	62		A	60
30	38	30	28	62		A	60
31	37		29	60	30	A	75
32	36	30	30	60		A	42
33	35	30	31	59		A	60

\* The columns as numbered indicate 1, district number, 2, approximate latitude, 3, minimal seasonal angle of sun (June), 4, distance from zenith of angle of sun in June, 5, weather bureau station from which figures are taken for ratio of June precipitation to annual precipitation A, Auckland, C, Christchurch, H, Hokitika, W, Wellington, 6, annual precipitation in inches, 7, calculated June precipitation, 8, radiation index derived from plotting distance from zenith of angle of sun in June (column 4) and calculated June precipitation (column 7) in chart 5

In column 5, Hokitika was selected as the standard for the ratios in districts 1, 2 and 3 because of the statement in the Encyclopaedia Britannica (fourteenth edition) that, at Invercargill, like Hokitika, spring is often wettest, rather than like Dunedin and Lincoln near Christchurch, where the total rainfall is generally distributed through the year. However, the distinctions are not great, as shown by the following ratios of June precipitation to annual precipitation: Auckland, 11 per cent, Christchurch, 10.5 per cent, Hokitika, 8.3 per cent, Wellington, 10 per cent.

† According to Hercus, Benson and Carter, the rainfall in district 9, South Canterbury, varies considerably in different parts of the district. The inference from their comments on district 10, Christchurch, and district 12, North Canterbury, is that there is a similar variation in these districts. The figure 70 used in the table to represent the annual rainfall in each of these three districts is the mean of the figures given by Hercus, Benson and Carter for the area of greatest rainfall (40 to 100 inches), as the high incidence of goiter in these districts suggests that for purposes of correlation the greatest permissible value be assigned to supposed goiter producing factors. However, the procedure involves statistical practice that is open to criticism.

were thus available. It is, of course, evident that, with these several substitutions, no actual measurement of depletion has been arrived at, and that as an index the estimate is only approximate at best. This value is referred to as the radiation index, and will be applied to each of the districts of New Zealand described by Hercus, Benson and Carter (charts 15 and 16). The data are summarized in table 2.



Hercus, Benson and Carter regarded their investigation of the amount of iodine in the soil as a study of the "soil of plant food, and therefore, indirectly, of human food" They concluded that "the hypothesis that goitre is caused by a deficiency of iodine in the diet has been fully sustained by the present investigation" They stated further "Reasons have been deduced also for believing that a relation holds between the incidence of goiter and the distribution of geological formations (as determining the nature of the soil) in New Zealand,

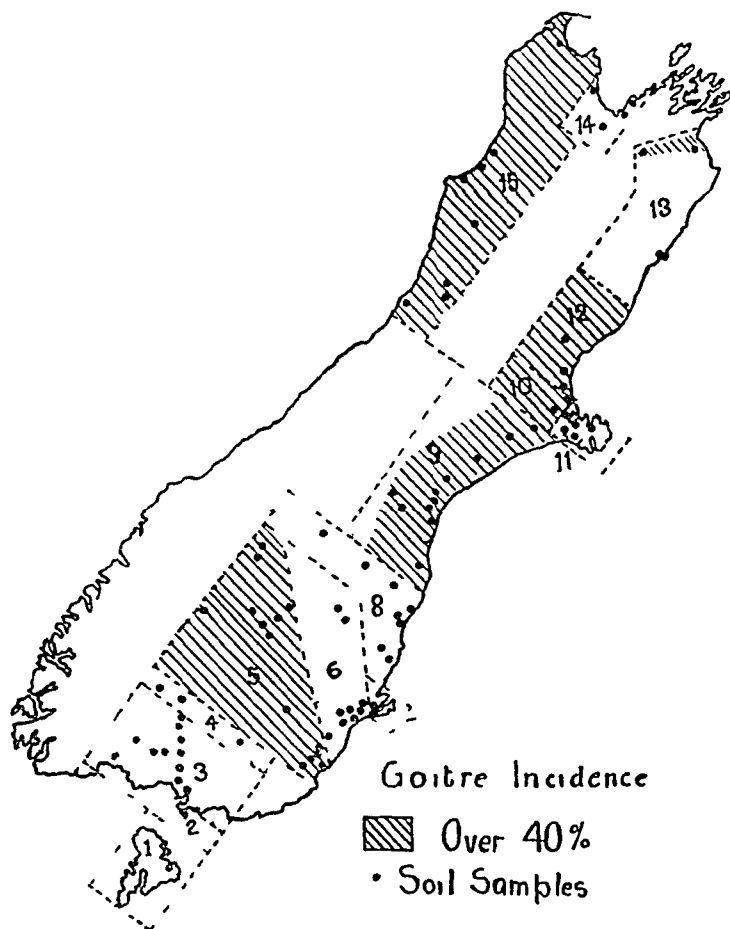


Chart 15—Districts of goiter incidence and localities of analyzed soils in New Zealand, South Island (After Hercus, Benson and Carter)

Switzerland, and perhaps in other countries" As supplementary to their study, in the present article consideration will be given to a possible influence of solar radiation on the iodine content of the soil and on the incidence of endemic goiter in New Zealand

Chart 17 reproduces the curves of Hercus and his co-workers, showing the relationship between the average amount of iodine in the soils and the regional incidence of goiter among school children and military recruits in New Zealand Only the former group is considered

in this article The curve is according to the formula  $y = \frac{360}{x} + 6$  when y equals goiter and x equals iodine<sup>37</sup>

For reference charts 15, 16, 18 and 19, from Hercus, Benson and Carter, are reproduced

The geological data shown in these maps are more particularly detailed in a table prepared by Hercus, Benson and Carter of the amount of iodine in New Zealand soils of different origin and nature Their description of the classification of the different soils is as follows

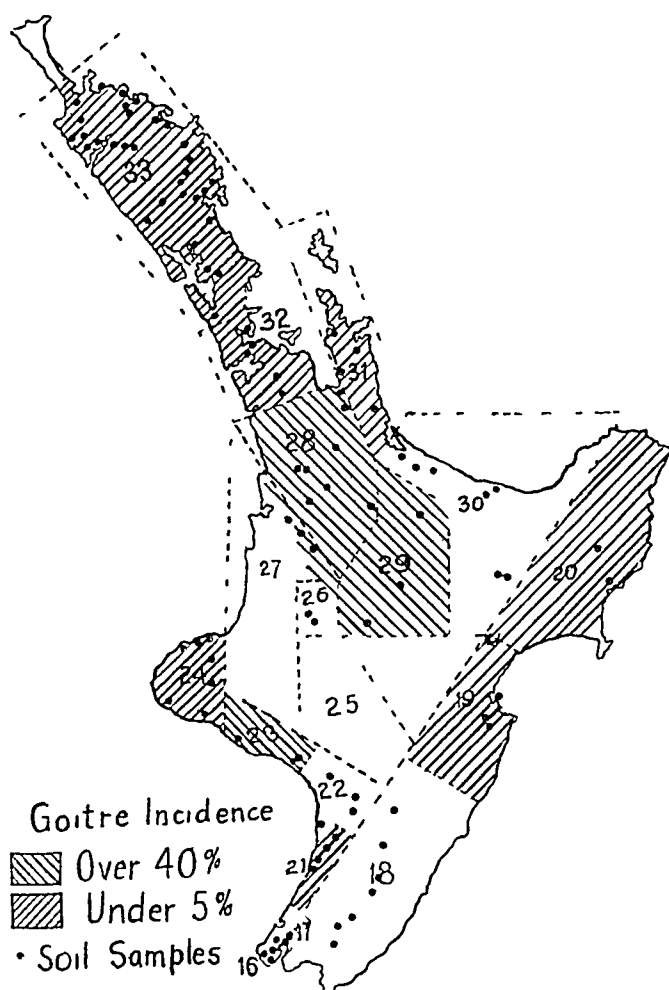


Chart 16—Districts of goiter incidence and localities of analyzed soils in New Zealand, North Island (After Hercus, Benson and Carter)

The main types of geological formations are indicated by the Roman numerals I to VI with suffixes according to the special variety indicated

I indicates plutonic rocks (which are not very widespread) Ig and In stand for the acid siliceous granites and basic norites respectively

II indicates mica schist, a much more widespread formation in the South Island

III indicates greywackes, argillites, etc., which form most of the highlands in New Zealand (They are mostly rocks of Mesozoic, but also in part of Paleozoic age) The mica schists were derived by metamorphism from rocks similar to these

IV indicates the younger Mesozoic and chiefly Tertiary sediments which rest on the schist and greywacke They are very varied, including conglomerates and

sandstones (sometimes with coal measures) (s), greensands (gs), claystone or marl (c), limestone (l), and volcanic tuffs (t) and are indicated respectively by IVs, IVgs, IVc, IVl, IVt

V indicates volcanic rocks which are either acid (rhyolite, rhyolite tuff and pumice or siliceous dacites), intermediate (andesite) or basic (basaltic) These are indicated by the signs Va, Vm, and Vb respectively Phonolites are comparatively rare and are indicated by Vp

VI indicates a widespread and varied group of post-Tertiary sediments of fluvatile, marine, or glacial origin They are classified thus

VIg (gravel), VIs (silt—mixed mud and sand)

VIsa (sands in beach or river), VIsw (swamp deposits)

VIds (dune sands), VIls (loess deposits), VIc (clays)

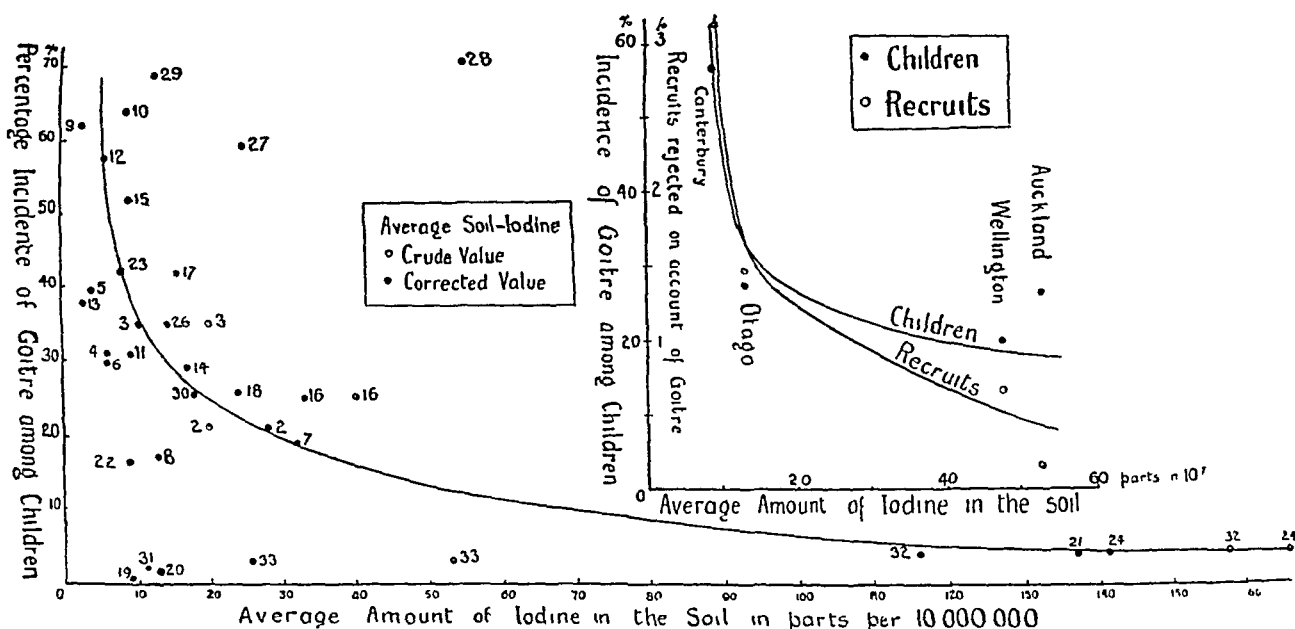


Chart 17—The relationship between the average amount of iodine in the soils and the regional incidence of goitre among school children and military recruits in New Zealand The figures by dots denote the districts indicated in table 2 (After Hercus, Benson and Carter)

Where it is of importance to indicate the formations immediately underlying the post-Tertiary cover this is done by writing the symbol for the upper formation above that of the lower, as the numerator and denominator in a fraction

From the weathering of these formations, various types of soil are derived, the natures of which are indicated by the symbols in the second column of the table The colour of the soil is indicated by capital letters B, black, Br, brown, R, red, G, gray, W, white, and Y, yellow, while the texture of the soil is indicated by small letters clayey (c), gritty (g), loamy (l), micaceous (m), sandy (sa), silty (s), stony (st), and where peaty or full of plant remains (v)

That portion of Hercus, Benson and Carter's paper relating to the various types of soils derived from the weathering of the geological formations has not been taken into consideration here The rest of the data in their table have been redistributed in table 3 so as to show

the different districts represented by soil of a given type and the number of samples from each district. In this way it is possible to compare the iodine content of samples of a given geological formation with other data related to the different districts.

In charts 20 to 28 a comparison has been made between the radiation index determined as described in the earlier part of this section

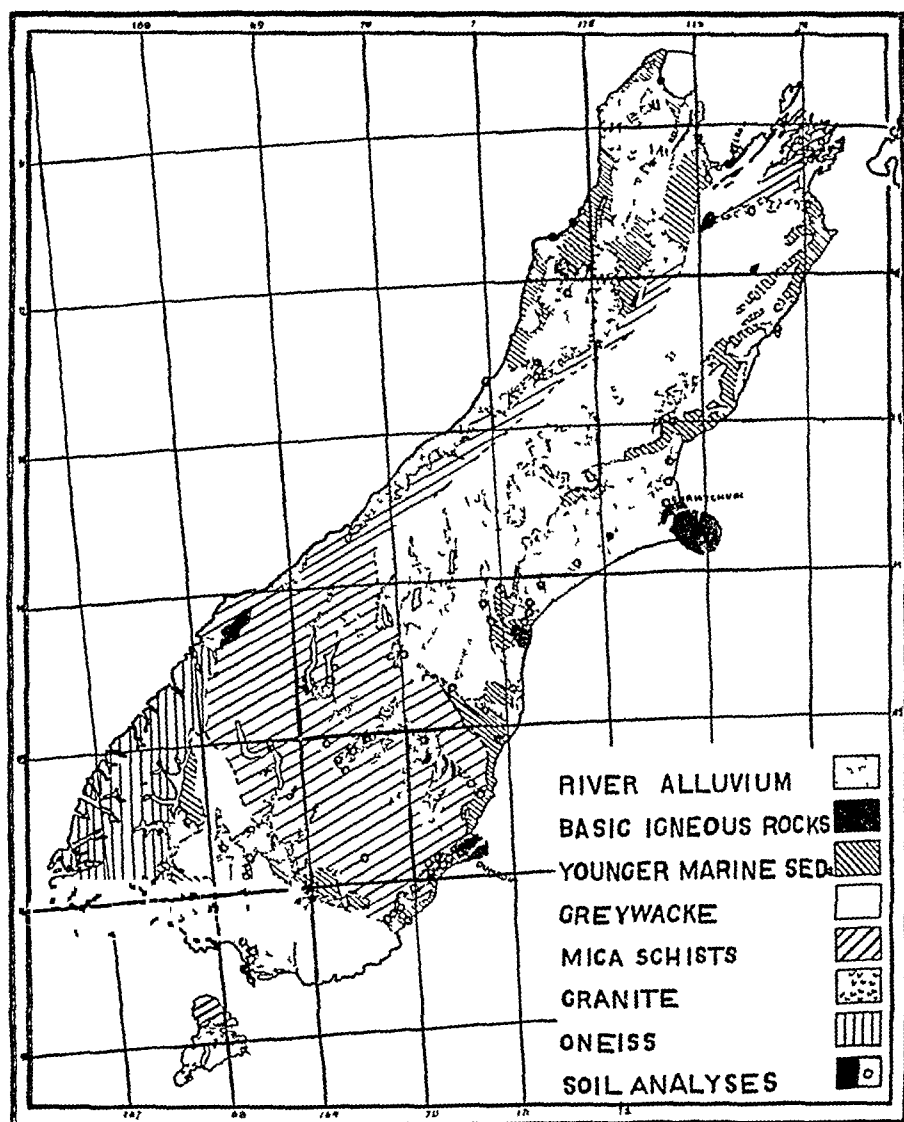


Chart 18—Geological sketch-map of New Zealand, South Island (After Hercus, Benson and Carter)

and the iodine content of the soil of a given geological formation. In some instances the districts represented by a given geological formation are too few to make a comparison profitable, and these have not been plotted. In chart 29 a comparison is made between the radiation index and the average iodine content of the soil of each district.

TABLE 3—Amount of Iodine (Parts per 10<sup>7</sup>) in New Zealand Soils of Different Origin and Nature (After Hercus, Benson and Carter.)

	Ig	VI Ig	In	II	VI II	III	VI III	IV	VI IV	Vb	VI Vb	Vm	VI Vm	Va	Vp	VI									
																g	gs	s	sa	sw	ds	ls	c	l	
1	127 (2)			6 (1)																					
2			20 (3)																						
3								10.8 (5)												3 (2)					
4																									
5				27 (16)	3.3 (30)	9.5 (2)	10 (2)	6.5 (8)																	
6				7 (1)	5 (3)			0.0 (1)		5 (2)															
7									18 (3)	21.3 (19)	10.6 (3)	14.6 (10)	18 (1)		25 (1)					62.3 (19)	2 (1)			15 (3)	
8						2 (1)		18.6 (10)		29 (2)	4 (2)					8.6 (5)		5.7 (7)						7 (2)	
9									3.6 (3)							0.0 (1)		3 (8)							
10																		10.6 (16)	1 (2)		0 (1)				
11											8.7 (8)														
12								6 (1)										5.2 (2)							
13								0.0 (1)										5 (2)		2 (1)					
14	4 (1)					11 (2)		38 (1)		38 (1)									10 (2)	10.5 (4)	42 (1)				
15		48 (1)																							
16						36.5 (8)															78 (2)				
17							16 (2)																		
18								25 (4)		47 (2)															



regardless of geological formation, according to the iodine content value used by Hercus, Benson and Carter in their paper<sup>38</sup>

In charts 30 to 40 a comparison is made between the radiation index and the incidence of endemic goiter, the districts being grouped in each chart so as to make the chart represent a single geological

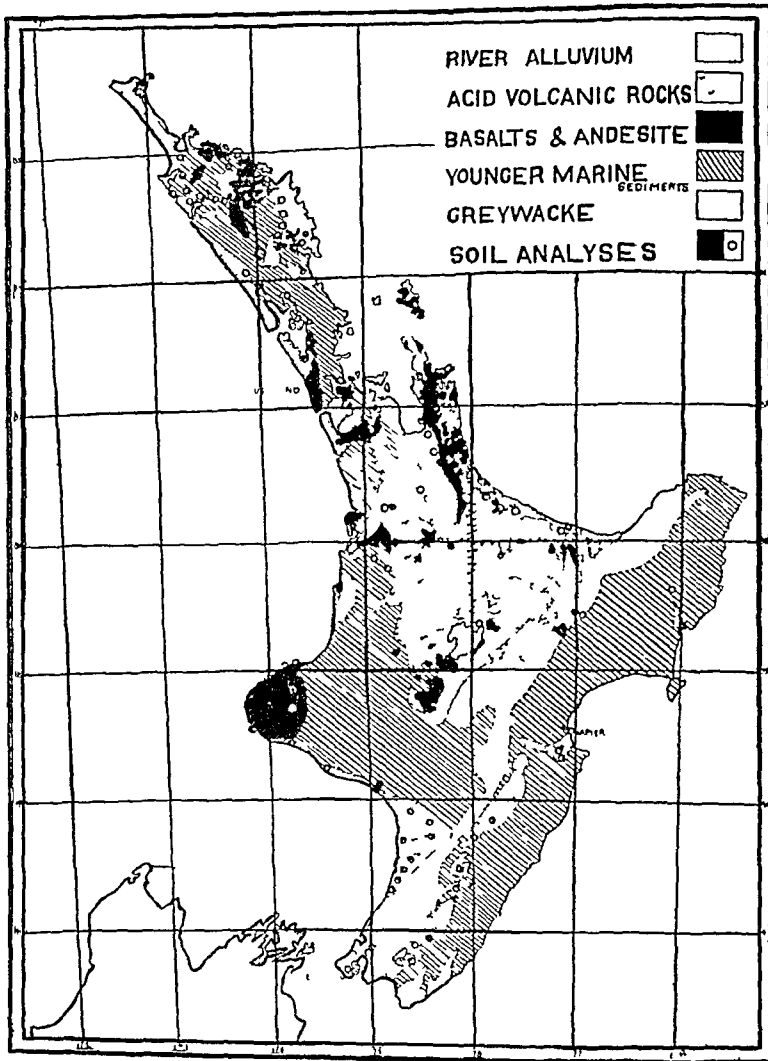


Chart 19—Geological sketch-map of New Zealand, North Island (After Hercus, Benson and Carter)

formation In chart 41 a comparison is made between the radiation index and the incidence of endemic goiter in each district, regardless of geological formation

<sup>38</sup> In a few instances these authors used a corrected value obtained by omitting from the calculation of the average abnormally large figures that they considered could not be taken as fairly representative of considerable areas of agricultural or pastoral land

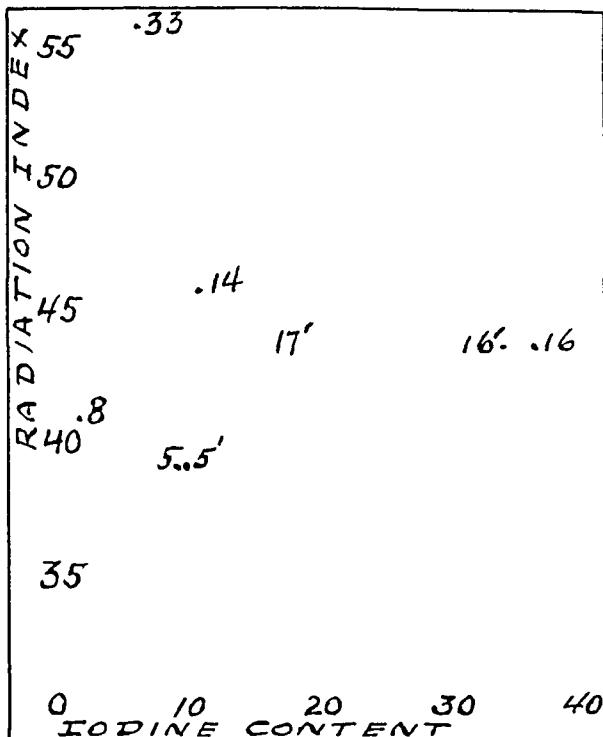


Chart 20—The relation of the radiation index to the amount of iodine in the soils of geological formations III (greywackes, argillites, etc, mostly rocks of Mesozoic but also in part of Paleozoic age) and  $\frac{VI}{III}$  (the same formation underlying a post-Tertiary cover), according to Hercus, Benson and Carter. The figures by dots denote districts. The character ' by figures denotes that the soil was obtained from a post-Tertiary cover of the earlier underlying formation.

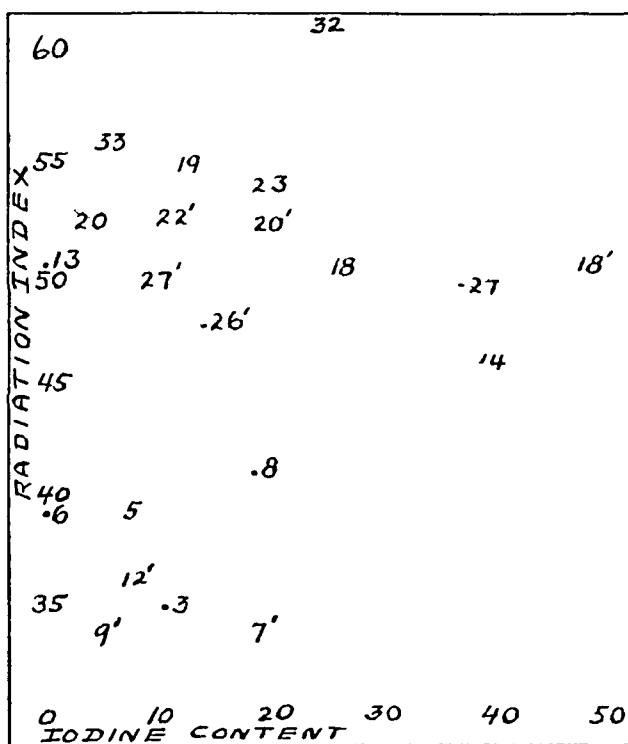


Chart 21—The relation of the radiation index to the amount of iodine in the soils of geological formations IV (younger Mesozoic and chiefly Tertiary sediments which rest on the schist and greywacke) and  $\frac{VI}{IV}$  (the same formation underlying a post-Tertiary cover), according to Hercus, Benson and Carter. The figures by dots denote districts. The character ' by the figures denotes that the soil was obtained from a post-Tertiary cover of the earlier underlying formation.



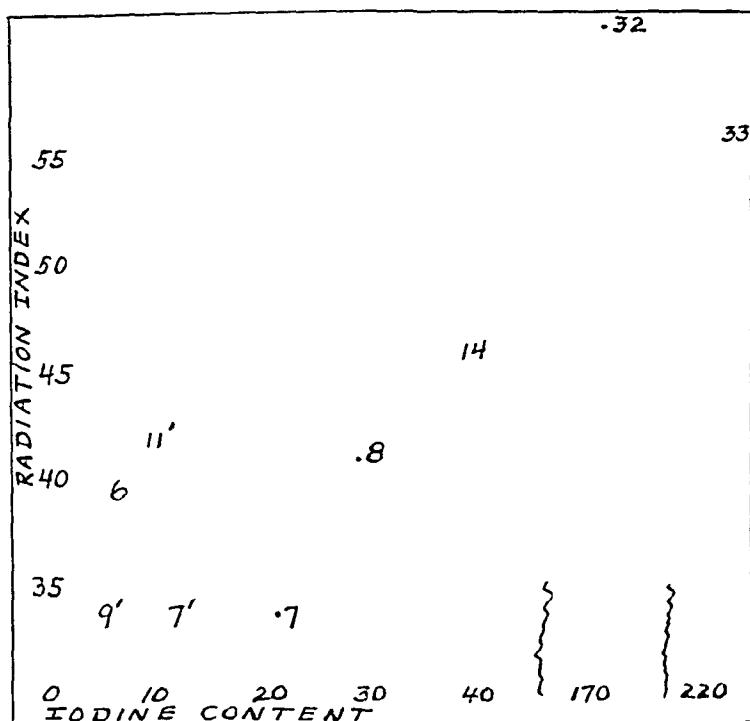


Chart 22—The relation of the radiation index to the amount of iodine in the soils of geological formations Vb (volcanic rocks which are basic-basaltic) and  $\frac{VI}{Vb}$  (the same formation underlying a post-Tertiary cover), according to Hercus, Benson and Carter. The figures by dots denote districts. The character ' by the figures denotes that the soil was obtained from a post-Tertiary cover of the earlier underlying formation.

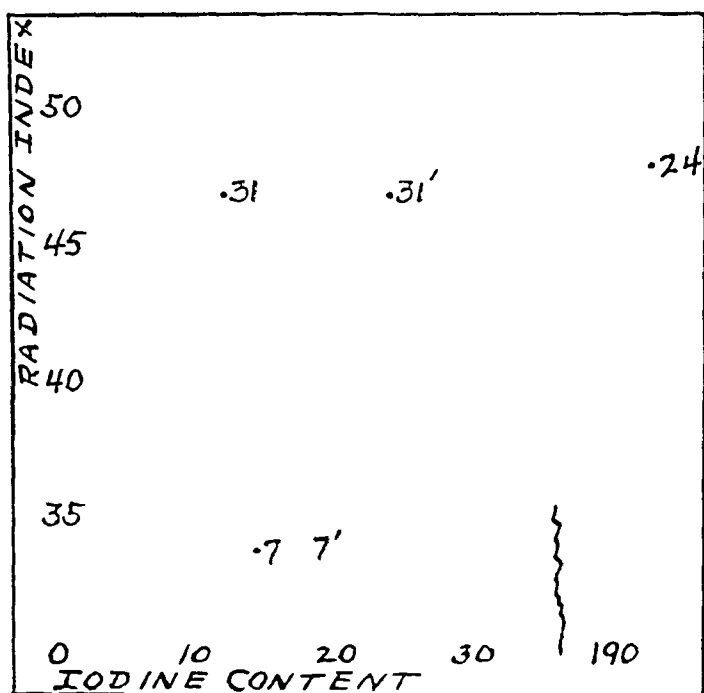


Chart 23—The relation of the radiation index to the amount of iodine in the soils of geological formations Vm (volcanic rocks which are intermediate—andesite) and  $\frac{VI}{Vm}$  (the same formation underlying a post-Tertiary cover), according to Hercus, Benson and Carter. The figures by dots denote districts. The character ' by the figures denotes that the soil was obtained from a post-Tertiary cover of the earlier underlying formation.

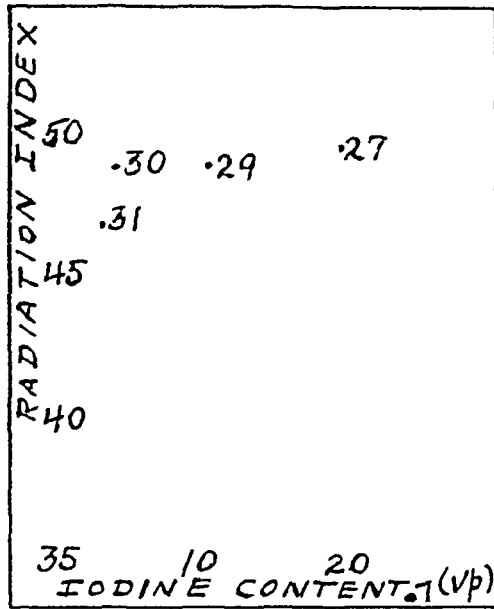


Chart 24—The relation of the radiation index to the amount of iodine in the soils of geological formation Va (volcanic rocks that are acid-rhyolite, rhyolite tuff and pumice or siliceous dacites), according to Hercus, Benson and Carter The figures by dots denote districts

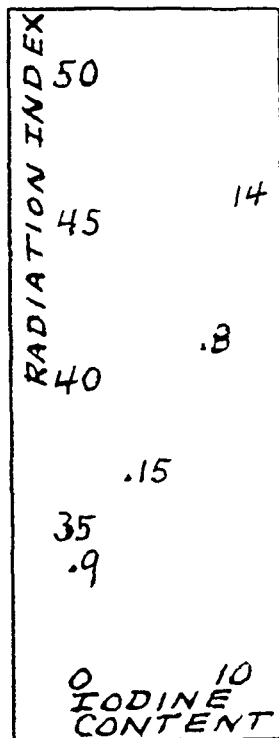


Chart 25—The relation of the radiation index to the amount of iodine in the soils of geological formation VIg (gravel from post-Tertiary sediments of fluvatile, marine or glacial origin), according to Hercus, Benson and Carter The figures by dots denote districts

Examination of charts 20 to 41 appears to warrant the notations in table 4

Generalizing from table 4, it may be said with reference to the geological formations from which relatively large numbers of samples were examined that there is seen some tendency to correlation between

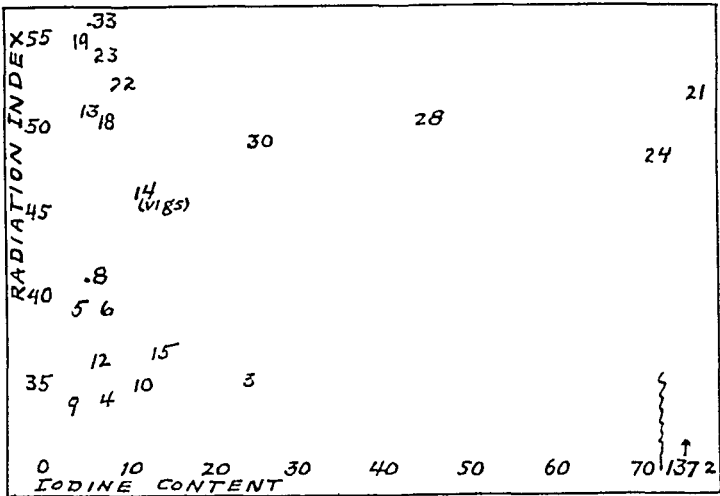


Chart 26 —The relation of the radiation index to the amount of iodine in the soils of geological formation VIs (silts—mixed mud and sand—from post-Tertiary sediments of fluvatile, marine or glacial origin), according to Hercus, Benson and Carter The figures by dots denote districts

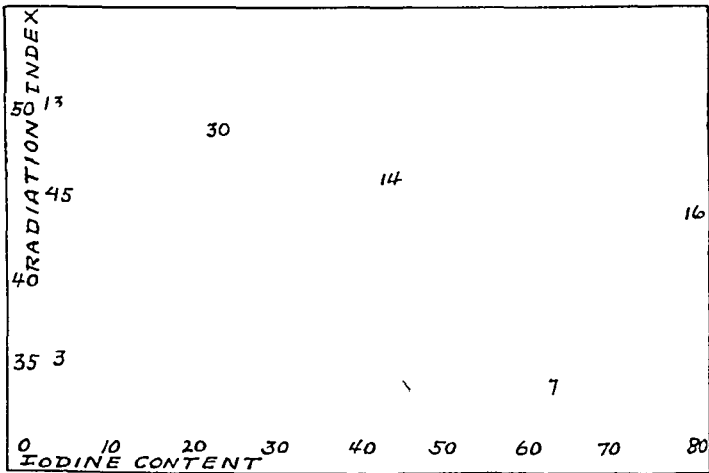


Chart 27 —The relation of the radiation index to the amount of iodine in the soils of geological formation VIsw (swamp deposits from post-Tertiary sediments of fluvatile, marine or glacial origin), according to Hercus, Benson and Carter The figures by dots denote districts

the radiation index and the iodine content of the soil of a given geological formation, and also between the radiation index and the iodine content of the soil of all the different geological formations taken as a

group, and it may be said with reference to all except four of the geological formations that there is seen some tendency to inverse correlation between the incidence of goiter and the radiation index. In

TABLE 4—*Notations from Examination of Charts 20 to 41\**

Chart	Geological Formation	Correlation Between	
		Radiation Index and Iodine Content of the Soil	Chart Incidence of Goiter and Radiation Index (Inverse)
20	II	None	None (only two districts, with same radiation index)
	VI		
	II		
	III		
21	VI	None	30 Some (only four districts)
	III		
	IV		
22	VI	Some	31 Some (districts 13, 23 and 27 high in goiter)
	IV		
	Vb		
23	VI	Some	32 Some (district 7 low and district 27 high in goiter)
	Vb		
	Vm		
24	VI	None	33 Some (district 7 low in goiter)
	Vm		
25	Va	None	34 Some (district 7 low in goiter)
26	VIg	Some	35 Some
27	VIsw	Some (a group of five districts in North Island low in iodine)	36 None
28	VIsw	None	37 None
29	VIsw	None	38 Some (districts 13, 23 and 25 high in goiter)
30	VIsw	None	39 None
	VIsw		
31	VIsw	None	40 None (only four districts, district 7 low, and district 23 high in goiter)
	VIsw		
32	VIsw	None	41 Some (districts 2 and 7 low, and districts 23, 27, 28 and 29 high in goiter)
	VIsw		
33	VIsw	None	
	VIsw		
34	VIsw	None	
	VIsw		
35	VIsw	None	
	VIsw		
36	VIsw	None	
	VIsw		
37	VIsw	None	
	VIsw		
38	VIsw	None	
	VIsw		
39	VIsw	None	
	VIsw		
40	VIsw	None	
	VIsw		
41	VIsw	None	
	VIsw		

\* Districts low in goiter (relatively high in iodine)

2 "The only inhabited area of basic plutonic rock in New Zealand" (Hercus, Benson and Carter)

7 The only district from which the samples of soil were predominantly from geological formation VIsw (swamp deposits from post Tertiary sediments of fluvatile, marine or glacial origin), 19 samples

Districts high in goiter

13 "Not fully represented by the few soil samples and schools studied" (Hercus, Benson and Carter)

23 No comment

27, 28 and 29 See comments of Hercus, Benson and Carter questioning the accuracy of the data for these districts

each of the four geological formations excepted only a relatively small number of districts was represented. There is also seen some tendency to inverse correlation between the incidence of goiter and the radiation index of all the different geological formations taken as a group.

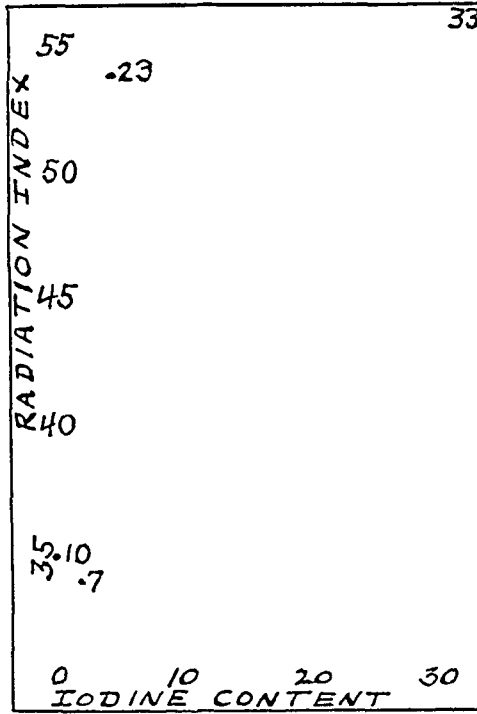


Chart 28—The relation of the radiation index to the amount of iodine in the soils of geological formation Vids (dune sands from post-Tertiary sediments of fluvatile, marine or glacial origin), according to Hercus, Benson and Carter The figures by dots denote districts

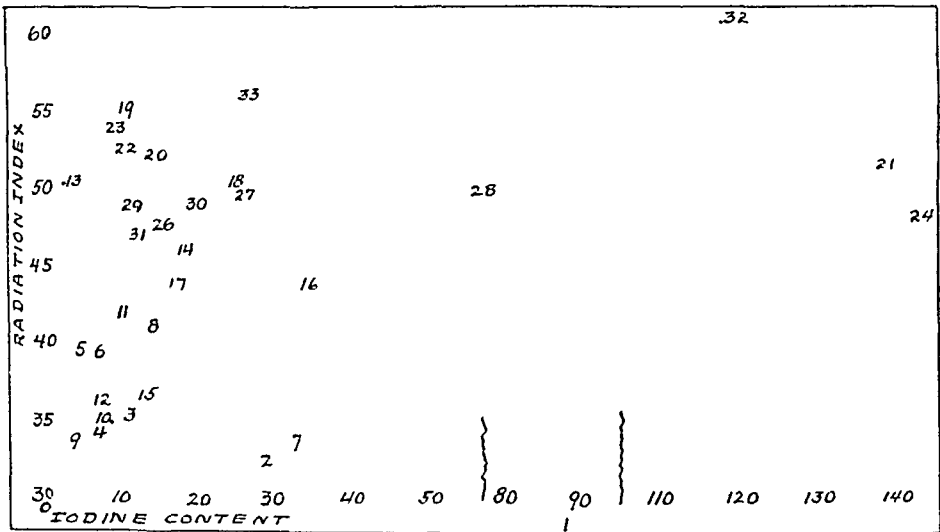


Chart 29—The relation of the radiation index to the amount of iodine in the soils of all geological formations as reported by Hercus, Benson and Carter The figures by dots denote districts

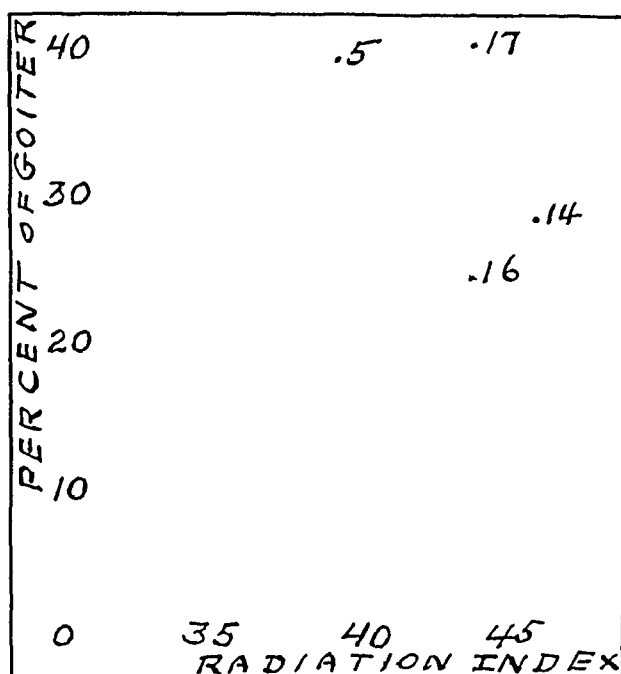


Chart 30—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soils from geological formations III (greywackes, argillites, etc., mostly rocks of Mesozoic but also in part of Paleozoic age) and  $\frac{VI}{III}$  (the same formation underlying a post-Tertiary cover), according to Hercus, Benson and Carter. The figures by dots denote districts.

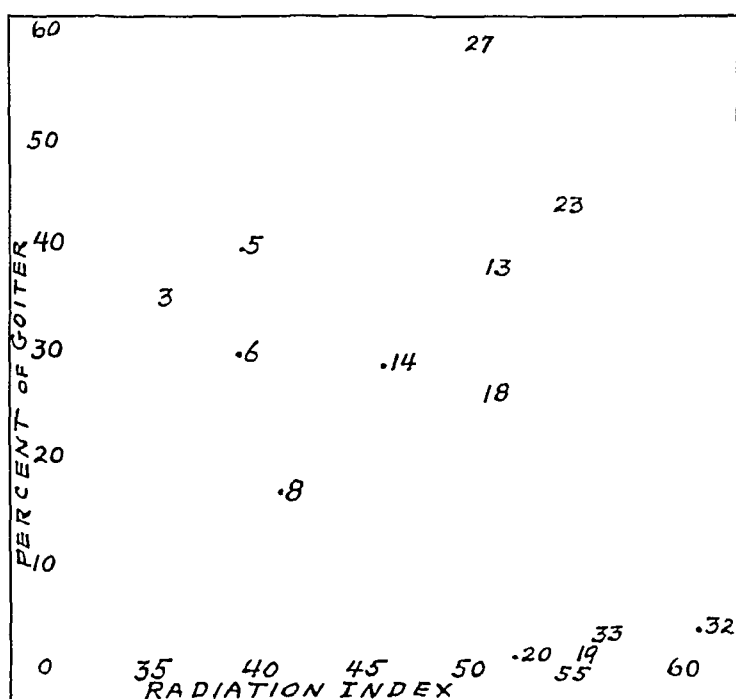


Chart 31—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formation IV (younger Mesozoic and chiefly Tertiary sediments which rest on the schist and greywacke) according to Hercus, Benson and Carter. The figures by dots denote districts.

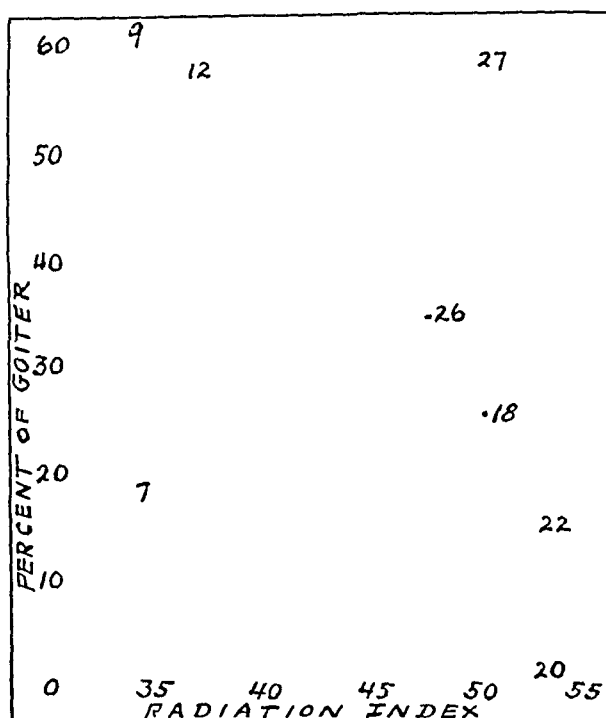


Chart 32—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formation  $\frac{VI}{IV}$  (younger Mesozoic and chiefly Tertiary sediments which rest on the schist and greywacke and underlying a post-Tertiary cover), according to Hercus, Benson and Carter. The figures by dots denote districts.

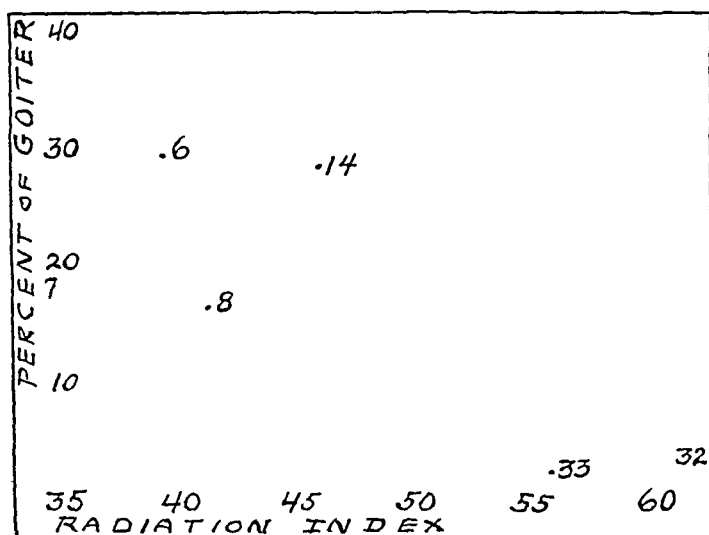


Chart 33—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formation Vb (volcanic rocks which are basic-basaltic), according to Hercus, Benson and Carter. The figures by dots denote districts.

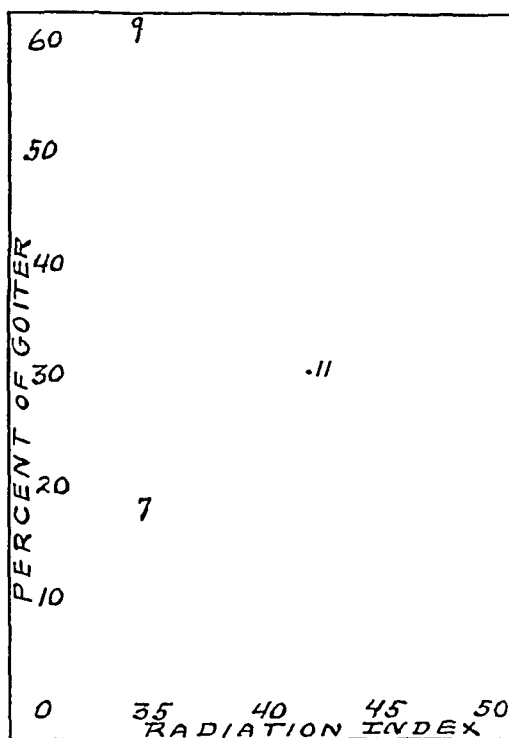


Chart 34—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formation  $\frac{VI}{Vb}$  (volcanic rocks which are basic-basaltic and underlying a post-Tertiary cover), according to Hercus, Benson and Carter. The figures by dots denote districts.

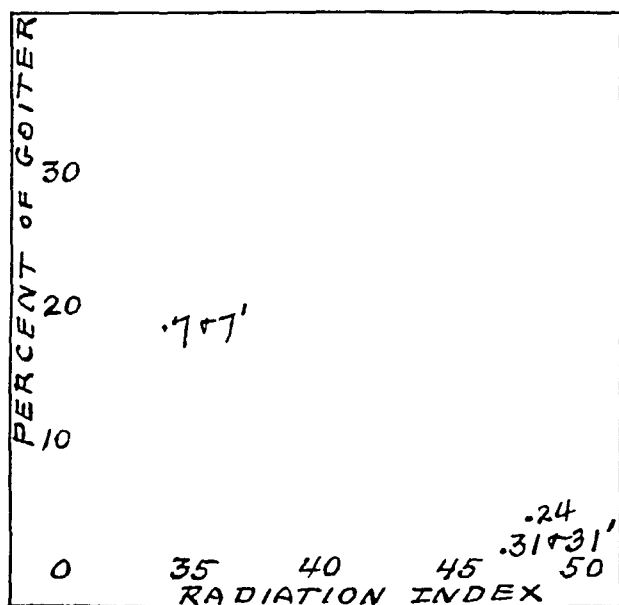


Chart 35—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formations  $V_m$  (volcanic rocks that are intermediate-andesite) and  $\frac{VI}{V_m}$  (the same formation underlying a post-Tertiary cover), according to Hercus, Benson and Carter. The figures by dots denote districts. The character ' by the figures denotes that the soil was obtained from a post-Tertiary cover of the earlier underlying formation.



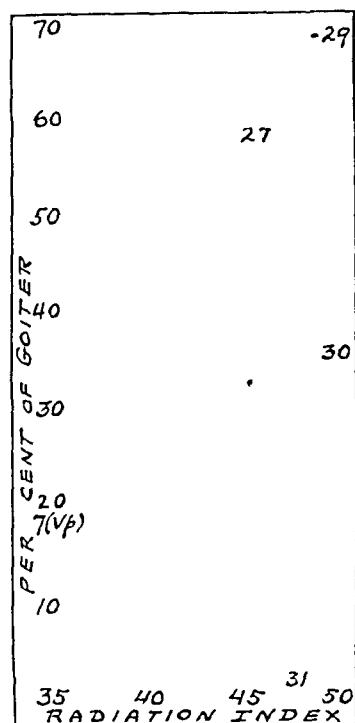


Chart 36—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formation Va (volcanic rocks that are acid-rhyolite, rhyolite tuff and pumice or siliceous dacites), according to Hercus, Benson and Carter. The figures by dots denote districts.

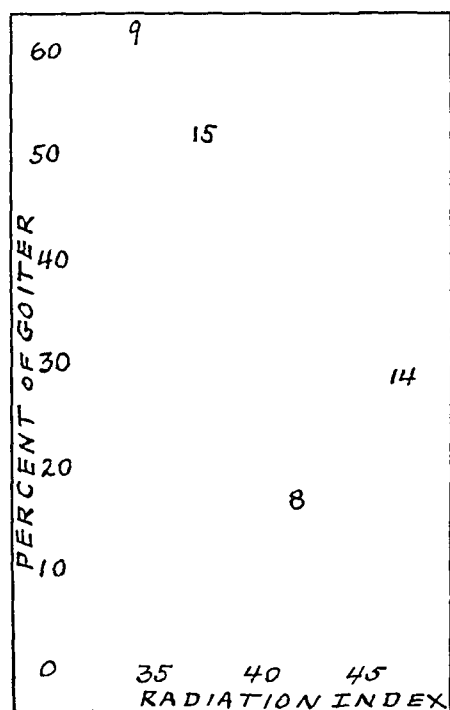


Chart 37—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formation VIg (gravel from post-Tertiary sediments of fluvatile, marine or glacial origin), according to Hercus, Benson and Carter. The figures by dots denote districts.

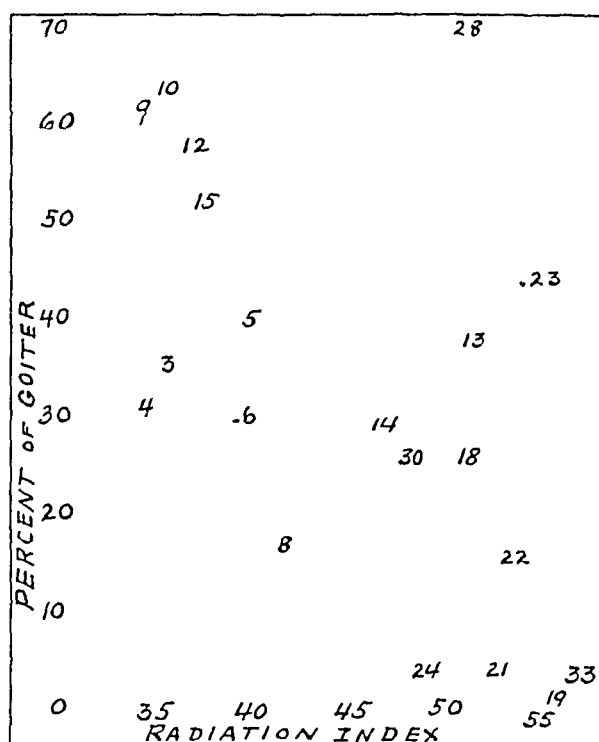


Chart 38—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formation VI (silts—mixed mud and sand—from post-Tertiary sediments of fluvatile, marine or glacial origin), according to Hercus, Benson and Carter. The figures by dots denote districts.

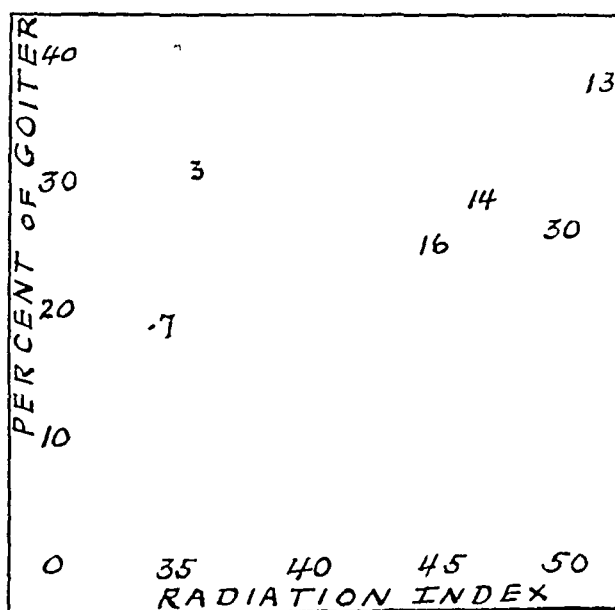


Chart 39—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formation VIsw (swamp deposits from post-Tertiary sediments of fluvatile, marine or glacial origin), according to Hercus, Benson and Carter. The figures by dots denote districts.

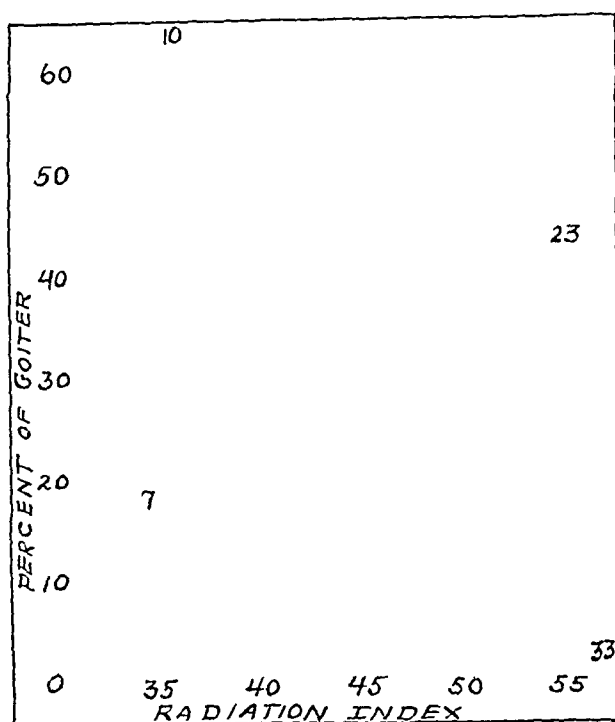


Chart 40—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from geological formation Vids (dune sands from post-Tertiary sediments of fluvatile, marine or glacial origin), according to Hercus, Benson and Carter. The figures by dots denote districts.

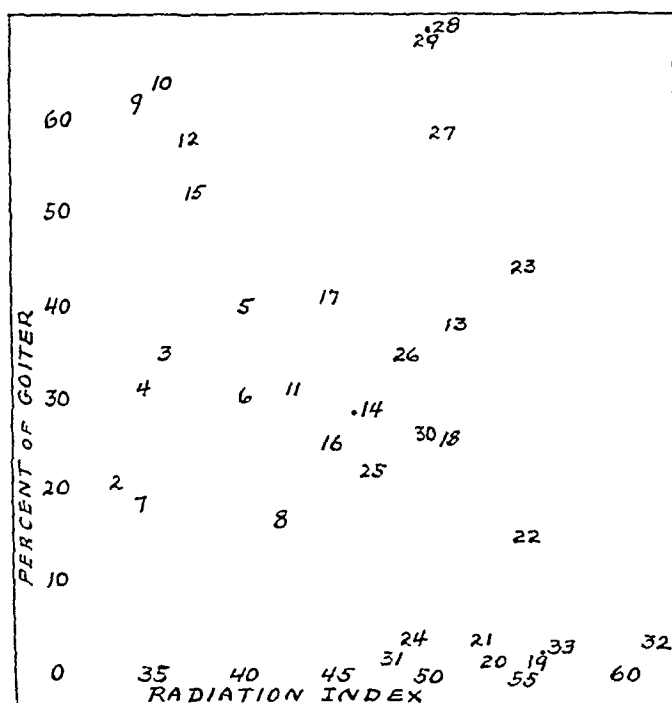


Chart 41—The relation of the incidence of goiter to the radiation index in districts from which were obtained samples of soil from all geological formations as reported by Hercus, Benson and Carter. The figures by dots denote districts.

The correlation referred to between the radiation index and the iodine content of the soil is direct, and that between the incidence of goiter and the radiation index is inverse, as is the correlation between the incidence of goiter and the iodine content of the soil. It appears, therefore, that in New Zealand solar radiation tends to decrease the incidence of endemic goiter.

#### CONCLUSIONS

The data in this section appear to support the conclusions in the two former sections dealing with endemic goiter in the United States and in India, respectively, namely, that a deficiency in solar radiation tends to a deficiency of the iodine content of the thyroid gland due to a lack of irradiation of the air, soil, food, drinking water or the skin of the animal organism, tending to an increased prevalence of endemic goiter.

In addition, with regard to several different geological formations in New Zealand, the iodine content of the soil appears to be roughly in proportion to solar radiation.

With regard to at least one type of geological formation (silts—mixed mud and sand—from post-Tertiary sediments of fluvatile, marine or glacial origin), the districts with a low iodine content of the soil derived from this geological formation (less than 13 parts in  $10^7$ ) show an incidence of endemic goiter in fairly close inverse proportion to the radiation index, suggesting that solar radiation tends to decrease the prevalence of endemic goiter in areas where the iodine content of the soil is low.

#### IV THE RELATION OF SOLAR RADIATION TO THE IODINE OF POTATOES AND THE DISTRIBUTION AND PREVALENCE OF ENDEMIC GOITER IN SOUTH CAROLINA

In sections I and II data were presented that appeared to suggest that a deficiency of solar radiation tends to an increased prevalence of endemic goiter, and in section III data were presented that not only support this conclusion, but in addition seem to suggest that, in New Zealand, the iodine content of the soil appears to be roughly in proportion to solar radiation. In this section, certain data relating to South Carolina as reported by Remington<sup>39</sup> and others will be examined with reference to the relation between solar radiation, the iodine of vegetables and goiter.

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<sup>39</sup> Remington, R. E. A Nutritional Research in the South, South M. J. 24 49 (Jan.) 1931.

Chart 42 shows topographical and soil areas in South Carolina,<sup>39</sup> table 5, goiter in South Carolina school children,<sup>40</sup> and table 6, the iodine content of potatoes in relation to the distance from the sea<sup>41</sup>

Data on solar radiation in South Carolina are available in the reports of the United States Weather Bureau as percentage of possible sunshine, summarized for the period of observation to and including 1920 in Bulletin W, and as "cloudiness" in the *Monthly Weather Review* of the bureau. The definition of these two terms and the methods of recording, as described by the bureau, are given elsewhere,<sup>1</sup> as also a notation to the effect that, though the percentage of sunshine and that of cloudiness are inversely related, they are not exactly so according to the methods of recording. On this account, in the present article, a mean of the two values, percentage of possible sunshine and cloudiness (reversed)<sup>42</sup> has

TABLE 5—*Goiter in the School Children of South Carolina*

	Number Examined	Percentage Enlarged
Coastal counties	5,684	2.7
Upper pine and sand hill counties	6,493	3.3
Piedmont counties	5,423	1.7

TABLE 6—*Iodine Content of Potatoes in Relation to the Distance from the Sea*

Distance from Sea in Miles	Number of Samples	Iodine Content (Average)
0-50	19	180
50-100	18	213
100-150	15	223
150-200	16	249
200	4	266

been used to represent solar radiation at the three South Carolina Weather Bureau stations for which the complete data are available: Charleston, in the coastal region and representing the Lower Pine Belt, Columbia, in the Sand Hills and Upper Pine Belt, and Greenville, in the Piedmont Region.

40 Hayne, J. A. Endemic Goiter and Its Relation to Iodine Content of Food, *Am J Pub Health* **19** 1111 (Oct.) 1929. Remington (footnote 39).

41 "The potato was chosen for this comparison because it is easily obtained everywhere, easily stored and shipped, and easily handled in the laboratory" (Remington, R. E., Culp, F. B., and von Kolnitz, H. The Potato as an Index of Iodine Distribution, *J Am Chem Soc* **51** 2942, 1929). Remington (footnote 39).

42 The figures used for cloudiness represent the average for the decade 1920-1929, inclusive, and the scale is, arbitrarily, twice that for possible sunshine. Cloudiness for the month of May at Columbia is represented by the figures for nine years only. The figures for possible sunshine, taken from Bulletin W, cover observations at Charleston for twenty-four years, at Columbia, for sixteen years, but at Greenville for only three, and sometimes four, years.

Chart 43 shows the solar radiation for the months of December, January and February to be greatest at Greenville, intermediate at Charleston and least at Columbia. This order is inverse to that of the incidence of goiter as reported by Hayne.

Chart 43 also shows the solar radiation for the months of July, August and September to be greatest at Greenville, intermediate at Columbia and least at Charleston. This order is the same as that of the iodine content of potatoes, as reported by Remington and his co-workers.

If this observation of a relationship between the iodine content of vegetables and solar radiation should prove on further investigation to

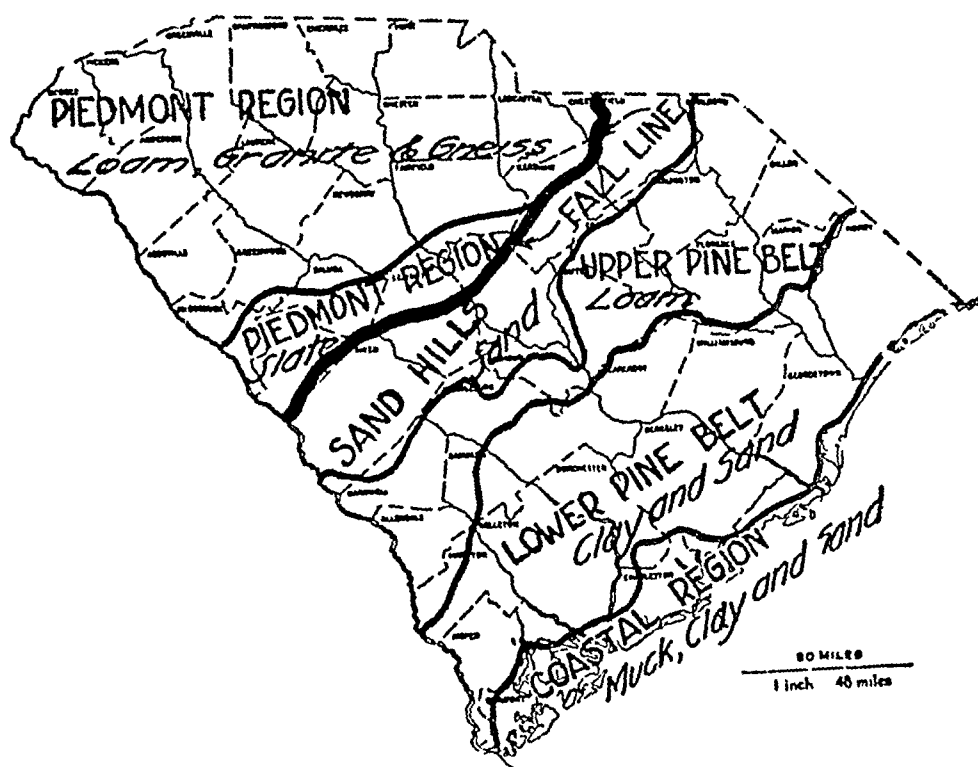


Chart 42—Topographical and soil areas in South Carolina (After Remington and his co-workers)

hold more generally, it would seem to be essentially linked with the tendency observed (section III) of the iodine content of the soil of New Zealand, as reported by Hercus, Benson and Carter, to be roughly in proportion to solar radiation at the time of the year for which the comparison was made (June—winter in New Zealand), regarding the soil as the soil of plant food.

That solar radiation during the months of July, August and September (in the north temperate zone) may have special significance in relation to the iodine content of vegetables is suggested by the following reported observations.

Von Fellenberg<sup>43</sup> in 1923 determined the iodine content of the salt from Schweizerhalle. In August, the salt contained no detectable iodine. On September 4 it contained 0.8 part per billion, and in October it rose to 7.7 parts per billion.

Veil and Sturm<sup>43</sup> studied the variations in the iodine content of blood. In the late summer and fall it was 128 parts per billion, and in the winter, 83 parts per billion.

Summer cabbage fed to rabbits had a much less marked goiter-producing tendency than cabbage grown in the late autumn.<sup>17</sup> Rabbits brought into the laboratory in the late fall or winter developed goiter.

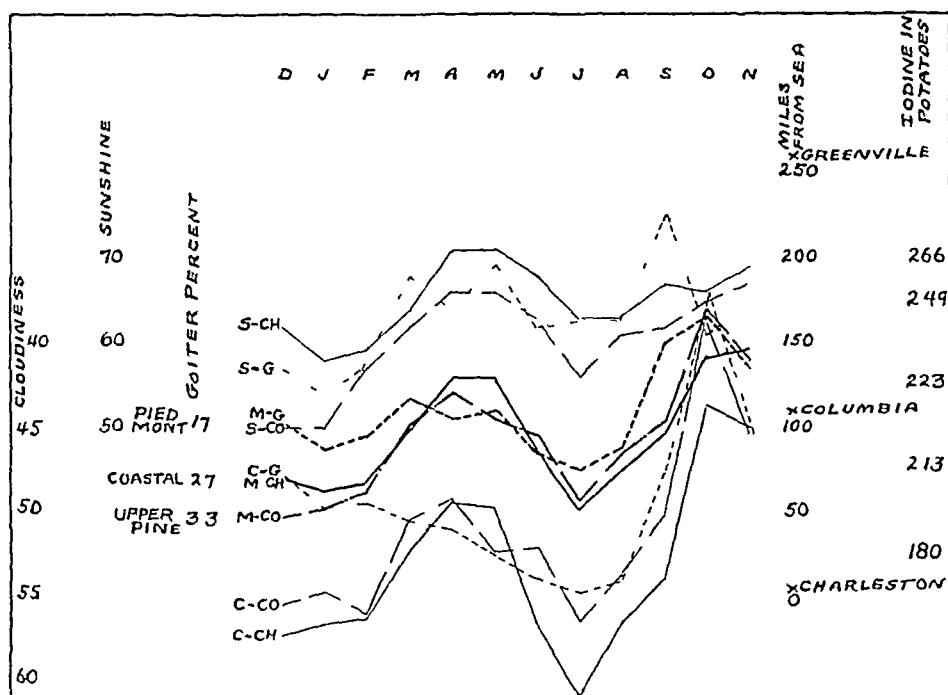


Chart 43—The solar radiation in South Carolina, by months. Curve S-CH indicates sunshine at Charleston, S-CO, sunshine at Columbia, S-G, sunshine at Greenville, C-CH, cloudiness at Charleston, C-CO, cloudiness at Columbia, C-G, cloudiness at Greenville, M-CH, mean of sunshine and cloudiness at Charleston, M-CO, mean of sunshine and cloudiness at Columbia, M-G, mean of sunshine and cloudiness at Greenville. The chart also shows the percentage of goiter in school children in the three topographic and soil areas (not scaled), the iodine content of potatoes in relation to distance from the sea and the distance from the sea of Charleston, Columbia and Greenville, respectively.

on a cabbage diet much more promptly than those brought in during the spring and summer.<sup>16</sup> Similarly, some of the large goiters tended to decrease in size slightly during the spring and summer.

<sup>43</sup> Quoted by McClendon, J. F. The Distribution of Iodine with Special Reference to Goiter, *Physiol. Rev.* 7: 189, 1927.

The iodine content of the thyroid gland is low in the early spring,<sup>28</sup> and goiter shows its highest incidence in India at the end of the rainy season <sup>44</sup>

#### CONCLUSIONS

The data in this section appear to support the conclusions in the three former sections dealing with endemic goiter in the United States, India and New Zealand, respectively, namely, that a deficiency of solar radiation tends to a deficiency of the iodine content of the thyroid gland due to a lack of irradiation of the air, soil, food, drinking water or the skin of the animal organism, tending to an increased prevalence of goiter

In addition, the iodine content of potatoes in districts of South Carolina, according to the distance from the sea, appears to vary with solar radiation during the late summer months, suggesting that solar radiation at this period of the year may have some influence on the iodine content of vegetables

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44 McCarrison (footnote 31) Stott, Bhatia, Lal and Rai (footnote 33)



# EFFECTS OF PROLONGED LIVER DIETARY IN PERNICIOUS ANEMIA

CASE REPORTS OF THREE PATIENTS RECEIVING LIVER THERAPY  
FOR NINE AND A HALF, EIGHT AND SEVEN YEARS,  
RESPECTIVELY

R B GIBSON, PH D  
AND  
W M FOWLER, MD  
IOWA CITY

More than ten years ago, Gibson and Howard<sup>1</sup> undertook a study of the chemical pathology and metabolism of pernicious anemia. Eleven cases along with four cases of other types of anemia were reported. An experimental diet consisting of fruits, green vegetables, lima beans, egg yolk and liver (100 Gm or more daily) was employed. This diet induced favorable retention of iron and nitrogen and enhanced the remissions in pernicious anemia, beginning in the fall of 1921 it was prescribed as a routine measure in our service, along with other recognized measures employed to promote hematogenesis. The patients were given specific dietary instruction when discharged. The use of such a diet in the therapy for pernicious anemia was urged in that report.

During the present year, three of our patients who received the liver diet before liver therapy was accepted generally as a specific therapeutic procedure have returned to this hospital. One of them was included in the original experimental group (1921), the second first received liver therapy in the summer of 1923 and the third, in the spring of 1924. It seems of interest to give a description of these patients when they were seen initially, their history in the interim, and the present status of the disease.

Of the original eleven patients studied by the senior author, seven have died and three have not been traced. At that time it was difficult to convince both the patients and their own home physicians of the importance of the dietary therapy. One patient (case 9) who followed the instructions faithfully died in December, 1929, of a cerebral hemorrhage, there had been no recurrence of the anemia.

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1 Gibson, R B, and Howard, C P. Metabolic Studies in Pernicious Anemia, Arch Int Med **32** 1 (July) 1923. A preliminary report was read before the Central Interurban Clinical Club at Iowa City, April 23, 1921.

## REPORT OF CASES

CASE 1—*History*—W D, a white man, aged 55, entered the University Hospital on Oct 13, 1921, because of gastric distress, weakness, and numbness of the hands and feet. The gastric distress had been present for several years, but had increased in severity during the two years prior to admission. The weakness had become noticeable at about the time that the gastric distress had increased, and had progressed so rapidly that he had not been able to work for the preceding

TABLE 1—*Regeneration of the Blood of W D on Liver Dietary*

Admission	Date	Hemoglobin	Red Blood Cells	White Blood Cells	Comment
First	10/ 5/21	54	2,030,000	4,120	Polymorphonuclears 59, lymphocytes 40, basophils 1
	10/13/21	65	2,180,000	5,200	
	10/24/21	70	2,620,000	4,800	Transferred to metabolism ward
	10/31/21	70	3,260,000	5,200	
	11/ 8/21	70	3,180,000	4,100	In metabolism ward
	11/17/21		3,880,000	6,050	
	11/25/21	80	4,050,000	4,050	Polymorphonuclears 74, lymphocytes 22, transitionals 4
	12/ 5/21	75	3,920,000	5,800	
Second	11/ 3/22	87	2,600,000	3,650	Polymorphonuclears 66, lymphocytes 31, large monocytes 2, transitionals 1
	11/ 6/22	89	2,970,000	3,000	
	11/10/22	90	2,860,000		Transfusion
	11/15/22	80	2,800,000	5,100	
	11/16/22				
	11/18/22	82	3,000,000	9,000	
	11/19/22	85	3,400,000		
	11/27/22	104	4,100,000		Transfusion
	12/ 6/22		3,940,000		
	12/12/22	104	3,700,000		
	12/17/22		3,450,000		
	12/19/22				
	12/22/22		3,930,000	6,600	
	12/26/22	100	4,500,000		
	1/ 1/23	97	4,670,000		
Third	6/12/27	12	610,000	3,200	Transfusion
	6/15/27				
	6/17/27	16	820,000		5,150
	6/22/27	30	1,970,000		
	6/24/27	32	1,880,000		
	6/29/27	35	2,150,000		
	7/ 4/27	40	2,770,000		5,800
	7/ 9/27	45	2,610,000		
	7/16/27	60	3,240,000		
	7/19/27	63	3,580,000		
	7/22/27	71	4,140,000	5,800	
	7/27/27	73	4,090,000		

eight months. One month prior to admission to the hospital, the patient had several attacks of diarrhea and began to notice numbness and clumsiness of the extremities.

*Examination*—There was moderate pallor and slight icterus of the skin. The mucous membranes were pale, and the tongue was smooth and atrophic. The lungs were normal. The heart was of normal size, with a systolic murmur at the apex. The blood pressure was 90 systolic and 50 diastolic. The spleen could just be felt below the left costal margin. Neurologic examination revealed subacute combined sclerosis of the cord. Urinalysis gave normal results. Analysis of the gastric contents showed an absence of free hydrochloric acid and a total acidity of 9. The stomach and duodenum appeared normal on roentgen examination. The blood smears showed a marked variation in the size and shape of the red cells with macrocytes predominating.

*Course*—The patient was given the diet for pernicious anemia with liver at the time of admission. The blood counts and hemoglobin readings for this and each subsequent admission are given in table 1. He improved markedly, and he was discharged with dietary instructions on Dec 15, 1921.

*Second Admission*—On Nov 3, 1922, the patient returned to the hospital, stating that he had followed the instructions carefully for four months, his weight had increased from 129 to 156 pounds (58.5 to 70.8 Kg), and his general condition had been good. He then became negligent, the gastric distress reappeared, and he had an attack of diarrhea. The physical findings were similar to those on the previous admission. He was given the same diet, but during this admission he received two transfusions of blood. On Jan 2, 1923, he was again discharged with the same dietary instructions as before, and pills of ferrous carbonate, U S P, solution of potassium arsenite and dilute hydrochloric acid were prescribed.

*Third Admission*—Subsequent to his discharge in 1923, there was a remission that lasted for three years. During this time he followed his dietary instructions faithfully, and was able to do hard work on the farm. Later he became careless about taking liver, and in the spring of 1926, a recurrence of the anemia, jaundice and gastric distress occurred. He then improved somewhat, but was able to do only light work. For the eight weeks prior to the third admission he became progressively worse, the pallor, jaundice, weakness and gastric distress recurred. He returned to the hospital on June 12, with an erythrocyte count of 610,000. The gastric contents contained no free acid, and the total acidity was 0. There was paresthesia and lingual atrophy. He was again given the diet for pernicious anemia, pills of ferrous carbonate, U S P, solution of potassium arsenite and hydrochloric acid. Because of the extreme anemia he received a transfusion of blood three days after admission. He was discharged on July 26, 1927, greatly improved, and with the instructions and medication given him previously.

*Fourth Admission*—On March 20, 1931, the patient returned to the University Hospital at our request. Since his discharge in 1927, he had followed the diet closely and had persistently eaten liver. During this time he had been able to do the heaviest farm work without difficulty. There was slight numbness of the extremities, but this was not as troublesome as it had been on his first admission. He was now 64 years of age, well developed and nourished and without pallor or icterus. The tongue was somewhat smooth. The heart was normal in size, and there were no murmurs. The blood pressure was 126 systolic and 74 diastolic. The liver and spleen could not be felt. The neurologic findings were unchanged. The urine was normal. The gastric contents contained no free acid even after the administration of histamine, and the patient complained of gastric distress when hydrochloric acid was not given with his meals. Examination of the blood showed hemoglobin, 93 per cent, erythrocytes, 4,490,000, leukocytes, 5,400, and reticulocytes, 14 per cent. A test for renal function showed a variation in specific gravity of from 1.008 to 1.020, the day volume of urine was 870 cc, the night volume, 860 cc, and 72 per cent of phenolsulphonphthalein was excreted in two hours. Chemical examination of the blood gave normal results.

*CASE 2—History*—W H, a white man, aged 34 years, was admitted to the University Hospital on June 9, 1923, complaining of loss of weight and strength, shortness of breath and occasional edema of the ankles. The initial attack had occurred in November of the preceding year.

*Examination*—On admission there was marked pallor and slight icterus of the skin. The gums bled slightly, and there was distinct atrophy of the tongue. The liver and spleen were palpable. The pulse was 120, and the blood pressure, 116.

systolic and 56 diastolic Examination of the blood showed 29 per cent of hemoglobin, 730,000 erythrocytes and 3,100 leukocytes, with 39 per cent of lymphocytes Pallesthesia was 50 per cent of normal over the shins Two-point discrimination and knee jerks were diminished Gastric analysis showed an absence of free acid and a total acidity of only 4 The excretion of urobilin was increased The patient was placed on the diet for pernicious anemia and given dilute hydrochloric acid and solution of potassium arsenate and pills of ferrous carbonate, U S P He received two transfusions Improvement was rapid, and the patient gained 6 pounds (3.6 Kg) in weight while he was in the hospital He was discharged on July 24, 1923, with instructions to follow the prescribed diet and medication At that time hemoglobin was 72 per cent, erythrocytes, 4,220,000, and leukocytes 6,200 (table 2)

TABLE 2—*Regeneration of the Blood of W H on Liver Dietary*

Admission	Date	Hemoglobin	Red Blood Cells	White Blood Cells	Comment
First	6/ 9/23	29	730,000	3,100	
	6/11/23				Transfusion
	6/13/23	35	1,340,000		
	6/18/23				Transfusion
	6/21/23	30	2,230,000		
	6/30/23	65	2,940,000		
	7/ 6/23	67	3,320,000	7,600	
	7/12/23	68	3,380,000		
	7/18/23	68	3,720,000		
	7/24/23	72	4,220,000	6,200	
Second	11/10/24	55	2,150,000	5,150	Transfusion
	11/15/24				
	11/19/24	55	2,220,000	4,300	
	11/25/24	71	2,880,000		
	11/30/24	75	2,880,000	5,900	
	12/ 6/24	80	3,470,000	5,000	
Third	7/23/31	52	2,600,000	7,500	General diet Reticulocytes, 0.6 ventriculin started
	7/25/31				
	7/30/31	60	2,645,000	6,000	
	7/31/31				
	8/ 3/31	75	3,180,000		Reticulocytes, 17
	8/ 6/31	78	3,150,000		Reticulocytes, 3
	8/13/31	79	3,280,000	8,300	Discharged

*Second Admission*—The patient was admitted to the hospital again on Nov 10, 1924 He had followed his instructions carefully since his discharge, particularly in regard to eating liver and meat, which had been impressed on him He had felt well, resumed his occupation doing heavy labor, and had missed only two days of work until five weeks before this admission, when influenza developed He apparently recovered from this infection in a few days, but anemia developed, and he returned to our service The patient's skin was icteroid and pale The tongue was atrophic The physical and neurologic findings were similar to those noted on the preceding admission The hemoglobin was 55 per cent, erythrocytes, 2,150,000, and leukocytes, 5,150, with 50 per cent lymphocytes The blood smear showed the typical picture of pernicious anemia The patient was again given the diet for pernicious anemia and dilute hydrochloric acid, with solution of potassium arsenite and pills of ferrous carbonate, U S P He received one transfusion He was discharged on December 9, much improved, the last examination of the blood (December 6) showed hemoglobin, 80 per cent, erythrocytes, 3,470,000, and leukocytes, 5,000

*Third Admission*—The patient was admitted again on July 23, 1931, with anemia which had developed after a remission of almost six and a half years. Since his second admission he had eaten meat and liver practically every day. He had been able to work hard and had but little illness until the present condition. About four months before this admission, he "turned against liver" and had to discontinue it. Two months later he became weak, short of breath and noticed a tingling sensation in the extremities. He became so weak that he had to remain in bed for two months prior to admission to the hospital. The glossitis had persisted, and there was a slight icteric tint to the skin. The spleen was palpable, but the liver was not enlarged. Although the patient complained of more numbness and tingling in the extremities on this last admission, the vibratory sense, the two-point discrimination and the sense of position were about normal. The patellar and tendo achillis reflexes were absent. Analysis of the gastric contents showed an achlorhydria even after the administration of histamine. A test for renal function showed that the specific gravity varied from 1.013 to 1.016, with a day output of 625 cc. and a night output of 550 cc. The excretion of dye was normal. The uric acid was 6.6 mg., the urea nitrogen, 23.1 mg. and the creatinine, 1 mg. per hundred cubic centimeters. The patient was given ventriculin and responded satisfactorily to this therapy. The blood counts are given in table 2.

*CASE 3—History*—E. K., a white man, aged 53, was admitted to the University Hospital in April, 1924. Five years previous to this (1919) he had a period of weakness associated with anemia, which was followed by a complete remission lasting until 1921, when he had a similar spell of weakness with numbness of the hands and feet, some edema of the ankles, a sore tongue and gastric distress. Since 1921, he had these attacks every fall, each one being more severe than the preceding one. The relapse that brought the patient to the hospital began six months prior to admission.

Examination showed a marked pallor with an icteric tint to the skin and sclerae, but the general nutrition was surprisingly good. The tongue was pale and atrophic. There were a hemic murmur over the heart and a slight pitting edema of the feet and ankles. The edge of the spleen was just palpable. Neurologic examination showed a subacute combined sclerosis of the cord.

There was 20 per cent hemoglobin. The erythrocytes numbered 930,000 and showed marked anisocytosis, poikilocytosis, polychromatophilia and stippling. Several megalocytes were seen on the smear. (The complete series of blood counts is given in table 3.) There was no free hydrochloric acid in the gastric contents, and a series of roentgenograms of the gastro-intestinal tract showed a normal condition. Urobilin was increased in the urine and stools. The patient was placed on the regular diet for pernicious anemia, and given, in addition, dilute hydrochloric acid and solution of potassium arsenite. He was discharged on June 23, 1924, with instructions to live on the aforementioned diet, eating liver every day.

*Second Admission*—The patient returned to the hospital in February, 1925, with essentially the same physical findings as on the previous admission. He had not followed his dietary instructions after the first two months following his discharge and began to notice increasing weakness two months prior to his return. He was given the same diet. The blood count on admission was hemoglobin, 53 per cent, erythrocytes, 2,050,000, and leukocytes, 4,400. At the time of discharge on April 10, 1924, the hemoglobin was 79 per cent and the erythrocytes, 3,000,000.

*Third Admission*—Following discharge, the patient felt well until September, 1925, when he had an attack of diarrhea associated with severe abdominal cramps and a temperature of 102 F. The abdominal distress persisted, and he gradually

became weaker. He had taken no medication since early the previous fall. When admitted to the hospital (March 9, 1926) the blood showed 39 per cent hemoglobin, 1,740,000 red blood cells and 2,000 white blood cells. Two transfusions of blood were administered during this admission. He was discharged on April 26, 1926, with 55 per cent hemoglobin, 3,220,000 red blood cells and 2,900 white blood cells.

*Fourth Admission*—The patient became convinced of the efficacy of the diet and ate cooked liver regularly, eating about one-fourth pound (113.4 Gm.) daily and doing without it only occasionally for very short periods. He had had no symptoms relative to the anemia since his discharge from the hospital in 1926, and had been doing heavy work regularly. The neurologic symptoms remained practically stationary. Seven weeks prior to admission, he first noticed polydipsia and polyuria, and glycosuria was found. Five days prior to admission he became comatose and received treatment at home, but he was given no insulin after recovering from the diabetic coma. He was sent to the hospital for diabetic management. He was well nourished, without pallor or icteric color. There was some sclerosis of the

TABLE 3—*Regeneration of the Blood of E. K., on Liver Dietary*

Admission	Date	Hemoglobin	Red Blood Cells	White Blood Cells	Comment
First	4/16/24	20	930,000	2,600	
	4/23/24	28	1,130,000	3,700	
	4/28/24	54	2,370,000	5,900	
	5/ 4/24	55	2,650,000	6,000	
	5/10/24	85	4,200,000	6,000	
	5/12/24				Fever severe stomatitis, unexplained
	5/14/24	90	4,230,000	5,300	
	5/24/24	60	2,600,000	4,000	
	5/29/24	80	3,600,000	4,000	
	6/ 2/24				Fever, temperature 104° F
	6/ 5/24	76	3,570,000	4,300	
	6/14/24	80	3,850,000	6,700	
	6/21/24	85	3,850,000	7,000	

vessels of the fundi, and the brachial vessels were moderately sclerotic. The tongue was smooth and reddened, but it was not sore. The lungs were normal. The heart was normal in size with a faint systolic murmur at the apex, the blood pressure was 128 systolic and 64 diastolic. The liver was not enlarged, but the edge of the spleen could just be felt beneath the left costal margin. No pulsation could be felt in either dorsalis pedis artery, but a good pulsation was felt in the posterior tibial arteries. The neurologic findings were unchanged. There were areas of leukoderma over the inner aspect of both wrists.

On admission there was 4 plus glycosuria, with a few casts and a trace of acetone. The urobilin in the urine was not increased. The modified Mosenthal test for renal function showed that the specific gravity varied from 1.003 to 1.016, with a normal ratio between the day and night output. Chemical examination of the blood showed uric acid, 4.2 mg., urea nitrogen, 13.3 mg., and creatinine, 1 mg. per hundred cubic centimeters. The van den Bergh test gave normal results, and the Wassermann test was negative. The blood sugar was 349 mg. per hundred cubic centimeters. The diabetes was controlled by the use of gradually decreasing doses of insulin, and on discharge the patient was receiving 10 units in the morning and 4 at night. The blood count showed 96 per cent hemoglobin (Sahl), 4,120,000 red blood cells, and 7,800 white blood cells, with a normal differential count. The hematocrit reading was 38 per cent. There was no free hydrochloric acid in the gastric contents.

## SUMMARY

Case reports of three patients with pernicious anemia for whom a liver dietary was prescribed from 1921 to 1924 along with other therapeutic measures to enhance and maintain the remissions are presented. These patients are undoubtedly the longest survivors among patients treated with liver for pernicious anemia whose records have been followed. While the liver dietary has been neglected at times by two patients (those in cases 1 and 3) with recurrence of the anemia, subsequent adherence to the dietary instructions has resulted in prolonged remissions, recovery of normal body strength and return to their occupations. A third patient (case 2) followed his dietary prescription consistently until four months previous to the last admission to the hospital (July, 1931) with the resulting attack of the anemia, a previous attack in 1924 followed an acute infection said to be influenza, so his remission had lasted six and one-half years. As has been observed in other cases by later workers with liver and active extracts (Minot,<sup>2</sup> Sturgis,<sup>3</sup> and others), the neurologic symptoms, the glossitis and achlorhydria in our three patients with pernicious anemia have remained essentially unimproved. For two of our patients, renal function is satisfactory, renal damage is evident in case 2, and possible injury attributable to the daily nucleoprotein intake cannot be excluded. But because of the progress all three patients have made and because of dietary factors in liver other than the substance effecting regeneration of the blood,<sup>4</sup> we feel that the dietary treatment of pernicious anemia should not be neglected, even though liver extracts are employed to induce and maintain the remissions.

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2 Minot, G. R., and Murphy, W. B. A Diet Rich in Liver in the Treatment of Pernicious Anemia, *J. A. M. A.* **89** 759 (Sept. 3) 1927.

3 Sturgis, C. C., Isaacs, R., and Riddle, M. C. The Treatment of Pernicious Anemia by Liver Feeding, *Surg., Gynec. & Obst.* **50** 234, 1930.

4 Dakin, H. D., West, R., and Howe, M. Further Note on a Substance in Liver Active in Pernicious Anemia, *Proc. Soc. Exper. Biol. & Med.* **28** 2, 1930.

# MYOCARDIAL INFARCTION OR GROSS FIBROSIS

## ANALYSIS OF ONE HUNDRED NECROPSIES

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AND

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The cases in this series were selected on the basis of gross post-mortem evidence of either recent infarction or fairly well circumscribed patches of fibrosis in the heart muscle. The fibrotic patches were all gross and were readily seen macroscopically, they were usually well margined. The large majority averaged at least 3 cm. in the largest diameter. It is believed that these fibrotic patches or scars in most cases probably represented areas of old infarction, particularly in view of the high incidence of associated coronary sclerosis. At any rate, as, regardless of their etiology, they presented a definite pathologic entity, they were grouped together in this series.

The one hundred cases selected comprised all cases in which the heart showed the aforementioned lesions in a series of nine hundred and forty-two necropsies performed at City Hospital from Jan. 3, 1928, to May 1, 1931. Thirty-two of the one hundred cases showed definite recent infarction, twenty-three of which also gave evidence of old myocardial scarring. The remaining sixty-eight cases were those that showed gross fibrosis alone. Thus 34 per cent of all autopsies performed during the period mentioned showed recent infarction, and 10.6 per cent showed either recent infarction or gross fibrosis, or both. This may seem an unusually high incidence, but the material at this hospital is in large part of a chronic nature, and includes a large number of patients past middle life suffering from arteriosclerotic heart disease.

### INCIDENCE

*Sex and Race*—Eighty-three patients were males, seventeen females, a ratio of almost 5:1. Parkinson and Bedford<sup>1</sup> in their autopsies performed in cases of cardiac infarction or mortal coronary thrombosis, found seventy-two males to eleven females.

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<sup>1</sup> Parkinson, J, and Bedford, D E. Cardiac Infarction and Coronary Thrombosis, *Lancet* **1** 4, 1928.



The racial distribution was as follows. Of the eighty-one white persons, sixty-six were males and fifteen females. Of the eighteen colored persons sixteen were males and two females. There was a Chinese male.

*Age*—The average age in all cases was 60.8 years. The distribution according to decades is indicated in table 1. In his outstanding monograph on coronary thrombosis, Levine<sup>2</sup> recorded forty-six autopsies, thirty-one performed on males and fifteen on females. The average age of the males was 61.3 years, that of the females, 61.8 years.

The youngest patient in our series was 28, the oldest 83 years old. The former case is worthy of note as being indicative of the early age at which coronary sclerosis and fibrotic patches of the type described may be found. The patient in this case died of uremia in the course of a chronic glomerulonephritis, with a superimposed terminal streptococcal bacteremia. At autopsy the heart weighed 450 Gm., and in the

TABLE 1—*Age Distribution According to Decades*

Age	Number of Cases
20 to 29	1
30 to 39	2
40 to 49	10
50 to 59	23
60 to 69	41
70 to 79	20
80 to 89	2
Not recorded	1

septum midway between its midportion and apex there was a fairly large, irregular white scar, which did not present, however, on either the epicardial or the endocardial surface. The coronary vessels were patent throughout, but the left anterior descending branch showed marked arteriosclerosis with narrowing of its lumen in the upper third. The remainder of this vessel, as well as the other coronary branches, showed only slight changes.

#### WEIGHT OF HEARTS

The average weight of the hearts in the entire series was 519 Gm. The smallest heart weighed 200 Gm., the largest, 925 Gm. The smallest heart was that of a man of 83 who showed old fibrotic lesions, aneurysmal dilatation of the left ventricle and liquefaction necrosis of a recent infarct.

The number of cases in each weight group is indicated in table 2.

It is seen at a glance that the large majority of hearts showed definite hypertrophy. The part played by old infarctions or fibrosis in inducing

<sup>2</sup> Levine, S. A. Coronary Thrombosis. Its Various Clinical Features, *Medicine* 8: 245, 1929.

hypertrophy of the rest of the heart muscle is a factor difficult to estimate because of the concomitant presence in most of the cases of other factors that may likewise have induced hypertrophy

The average weight of the hearts in each decade is interesting to note and is indicated in table 3

Though the differences here are not outstanding, there is nevertheless an appreciable decrease in weight after the fifth decade

TABLE 2—*Weight of Hearts in Series Reported*

Weight, Gm	Number of Cases
200 to 299	4
300 to 399	16
400 to 499	18
500 to 599	15
600 to 699	22
700 to 799	10
800 to 899	3
Over 900	1
Not recorded	11

TABLE 3—*Average Weight of Hearts in Each Decade*

Decade	Number of Cases	Average Weight of Heart, Gm
20 to 29	1	450
30 to 39	2	550
40 to 49	9	600
50 to 59	21	510
60 to 69	36	523
70 to 79	17	453
80 to 89	2	325

## LOCATION OF LESION

The thirty-two cases of recent infarction were distributed as follows

Left ventricle	16 cases
Left ventricle and interventricular septum	10 cases
Interventricular septum	3 cases
Apex of both right and left ventricles	1 case
Right ventricle and septum	1 case
Right and left ventricles and septum	1 case

The two last mentioned cases were both instances of right coronary occlusion

The associated old lesions in twenty-three of the thirty-two cases of recent infarction were distributed as follows

Left ventricle	8 cases
Left ventricle and interventricular septum	9 cases
Interventricular septum	5 cases
Right ventricle	1 case

The lesions of old infarction or fibrosis were situated as follows

Left ventricle	27 cases
Left ventricle and interventricular septum	24 cases
Interventricular septum	11 cases
Right and left ventricles	3 cases

In three cases the description was insufficient for localization

Thus it is seen that the large majority of lesions were found in the left ventricle or in the left ventricle and adjoining septum. However, it is noteworthy that in fourteen cases the lesions were confined to the septum exclusively and, as in many cases there was no endocardial or pericardial involvement, the importance of examination of this portion of the heart muscle is emphasized.

#### CORONARY VESSELS

*Sclerosis*—Twenty-one of the cases with recent infarction showed moderate to marked sclerosis of the coronary vessels, three, only slight sclerosis; three were reported as normal or with only minimal changes, while in five the description of the coronary vessels was lacking or inadequate.

Of the cases with old lesions, fifty-four showed moderate to marked sclerosis. In this group narrowing of the lumina of the vessels was marked in seventeen cases. Five cases showed only slight sclerosis. In four cases the vessels were normal or showed only minimal changes. In the remaining five cases, description was lacking or inadequate.

Thus of the ninety cases available for analysis, seventy-five, or approximately 83 per cent, showed moderate to marked sclerosis and eight, slight sclerosis, and in seven cases the vessels were practically normal grossly.

The sclerosis of the coronary vessels was by no means uniform in its distribution in all cases. It was often patchy throughout the same vessel, and in a few cases marked sclerosis was found in the left coronary artery and its branches with only minimal changes in the right coronary wall.

An interesting feature in one case was an aneurysmal dilatation of the right coronary artery.

*Thrombosis*—Thrombosis of the coronary arteries was noted in thirteen, or 40.7 per cent, of the cases with recent infarction and in eleven, or 16.2 per cent, of the cases with old lesions. Levine reported thrombosis in twenty-three of his forty-six autopsies, while in twelve others occlusion was due to the narrowing of the lumen of an arteriosclerotic vessel.

In our series the situation of the thrombus was as follows

Cases with recent infarction—

Anterior descending artery	9 cases
Posterior descending artery	1 case
Right coronary artery	1 case
Both right and left coronary arteries	2 cases

Cases with old lesions—

Anterior descending branch of left coronary artery	10 cases
Both right and left coronary arteries	1 case

Thus of the twenty-four cases in which coronary thrombosis could be demonstrated, the thrombosis occurred in the anterior descending coronary artery alone in nineteen cases and in conjunction with thrombosis elsewhere in the coronary circulation in three other cases.

In the case in which the right posterior descending coronary artery was thrombosed, the infarcted area involved the right ventricle and interventricular septum especially at the apex. In the wall of the right ventricle was a recent mural thrombus involving most of the apex. A small old lesion possibly of an old infarction was found in the wall of the left ventricle. This case also showed recent infarcted areas in both lungs.

In the other case of thrombosis of the right coronary artery the thrombus extended from just beyond the mouth of the artery to well toward the base of the left ventricle. The infarcted area coincided fairly well with the usual distribution of the right coronary artery. The posterior half of the interventricular septum was found to contain a large cavity filled with a fresh blood clot. This cavity extended into the adjacent ventricles, especially the right. Transection of the right ventricular wall revealed a yellow infarcted area with a hemorrhagic zone at its periphery in its posterior aspect. The posterior half of the left ventricle revealed a similar infarcted area. Unfortunately, the patient in this case died less than three hours after admission to the hospital, and so the available clinical data were scanty.

#### COMPLICATIONS

Mural ventricular thrombosis was noted in thirty-four cases. It occurred in sixteen, or 50 per cent, of the cases with recent infarction. In thirteen of these cases it was confined to the left ventricle, in the three remaining cases it involved both ventricles.

In the cases of old fibrosis, mural thrombosis was noted in eighteen, or 26.4 per cent. In seventeen of these cases, the condition was confined to the left ventricle and in one, to the right ventricle. In their series, Parkinson and Bedford reported the occurrence of intracardiac thrombosis in fourteen of eighty-three instances, Levine, in thirty-eight of his forty-six cases of coronary thrombosis.

Aneurysm of the left ventricle or distinct aneurysmal bulging was noted in five cases. Parkinson and Bedford likewise recorded five cases in their series of eighty-three. However, they also reported five cases with rupture of the heart. Levine found nine ruptured hearts in his series of forty-six cases. No cases of rupture of the ventricle were noted in this series.

Chronic adhesive pericarditis was noted in ten cases, only two of which were in the group with recent infarctions. In a case not included in the ten mentioned, acute suppurative pericarditis was associated with an old tuberculous lesion. Parkinson and Bedford reported eleven cases of pericarditis, an incidence of 13 per cent. Levine noted pericarditis in twenty-four of his forty-six cases.

Of the ten cases of pericarditis in the present series, mural ventricular thrombosis occurred in five.

Endocardial complication was thus much more common than epicardial, there were thirty-four cases of the former to ten of the latter.

Other interesting features were thrombosis of both the right and the left auricular appendages in two cases and of the right auricular appendage alone in one case.

One case previously described<sup>3</sup> as showing thrombosis of both the right and the left coronary arteries also showed a rupture of the left auricular wall.

#### RELATIONSHIP TO SYPHILIS

The Wassermann test was made for sixty-one of the eighty-two white patients. Only six had positive reactions. However in one case in which the Wassermann test was negative, and in five cases in which no test had been made, there was evidence of vascular syphilis at autopsy. Of the group of eighteen colored patients, four had positive Wassermann reactions and eleven negative ones. There was no report on the Wassermann test for three others. In this group three of the eleven cases in which the Wassermann test was negative showed evidence of vascular syphilis at autopsy.

The incidence of syphilis was thus higher in the colored group. The rôle of syphilis as an etiologic agent in infarction or fibrosis as described in this series is a questionable one. As the patients at this institution are drawn from the lower walks of life, a goodly number have syphilitic infections. In any event, in practically all the cases herein noted in which the Wassermann test was positive or evidence of vascular syphilis was found at autopsy, there was associated coronary sclerosis not syphilitic in nature.

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<sup>3</sup> Lisa, J. R., and Ring, A. A Case of Occlusion of Both Coronary Arteries with Rupture of the Auricle, *J. Lab. & Clin. Med.* **16** 1083 (Aug.) 1931.

## BLOOD PRESSURE AND ELECTROCARDIOGRAPHIC FINDINGS

Hypertension, the criterion of which was a systolic pressure of 150 or over, or a diastolic pressure of 100 or over, occurred in forty-five of seventy-three cases in which blood pressure readings were recorded, an incidence of approximately 60 per cent. Barnes and Ball,<sup>4</sup> using this criterion, noted hypertension in twenty-four of forty-two cases of myocardial infarction.

One or more electrocardiographic tracings were taken in twenty-four cases, eight with recent infarctions, six of which also showed old lesions. The findings are tabulated in the accompanying table. Digitalis as a possible factor in causing changes in the tracings, was eliminated in all but three cases.

## Rhythm

Normal sinus rhythm	11 cases
Normal sinus rhythm with extrasystoles	7 cases
Auricular fibrillation	5 cases
Idioventricular rhythm	1 case

## Conduction Time

Normal in seventeen of eighteen cases with normal sinus rhythm

## Axis Deviation

Left axis deviation	19 cases
No axis deviation	5 cases

## Q-R-S Complex

Abnormality (including notching, slurring, widening or low voltage in one or more leads)	17 cases
Normal	7 cases

## T Wave

Abnormality of the T wave (including inversion, isoelectricity or diphasic form) in one or more leads was noted in twenty-three of the twenty-four cases.

It is seen from the accompanying table that the most constant abnormality observed was that of the T wave. Willius and Barnes<sup>5</sup> noted T wave change in twenty-six of thirty-one cases of myocardial infarction. Left axis deviation was the next most frequent finding, occurring in nineteen of the twenty-four cases. Abnormality of the Q-R-S complex was frequent, occurring in seventeen cases. Pardee<sup>6</sup> noted an abnormal ventricular wave in 81 per cent of cases in which the clinical diagnosis was cardiac infarction. In our present series auricular fibrillation was noted in only five cases and complete block in one.

4 Barnes, A. R., and Ball, R. G. Proc. Staff Meet., Mayo Clin. **5**: 367 (Dec. 17) 1930.

5 Willius, F. A., and Barnes, A. R. Myocardial Infarction. An Electrocardiographic Study, J. Lab. & Clin. Med. **10**: 427 (March) 1925.

6 Pardee, H. E. B. Heart Disease and Abnormal Electrocardiograms, Am. J. M. Sc. **169**: 270 (Feb.) 1925.

## CLINICAL PICTURE AND IMMEDIATE CAUSE OF DEATH

A classification of the cases according to their outstanding symptomatology and clinical course revealed that they might be grouped into two major classes, namely (1) cardiac and (2) noncardiac in which the clinical syndrome involved primarily some other organ

There were fifty-six cases in the cardiac group. They could be somewhat arbitrarily divided according to outstanding symptomatology into the following groups: (a) anginal, (b) dyspneic and (c) congestive failure and (d) a combined group in which the clinical course was marked by a transition from one of the preceding groups to another. To illustrate the basis of this classification the following four cases are reported in brief:

*Anginal Type*—In a white man, the onset of the condition occurred with sudden severe epigastric pain when he was 65 years old. Subsequently recurrent attacks of precordial pain and dyspnea developed, they lasted several days, occurred at fairly frequent intervals, and became more frequent. The blood pressure was 190 systolic and 140 diastolic. Death occurred during an anginal attack one year later. Autopsy revealed acute cardiac infarction with old fibrosis associated with coronary sclerosis.

*Dyspneic Type*—In a white woman, aged 70, acute paroxysmal attacks of dyspnea, orthopnea and transient edema of the ankles developed. The blood pressure was 170 systolic and 90 diastolic. The attacks lasted from one to two days, with free intervals between. She died at the end of a dyspneic attack which had lasted for about a week. The cardiac condition was of five months' duration. Autopsy revealed an old cardiac infarction, coronary sclerosis and canalized thrombosis of the anterior descending artery.

*Congestive Failure Type*—In a white woman, aged 66, the onset of the condition was gradual, with weakness, edema of the ankles and dyspnea on exertion, which later became orthopnea, and cyanosis and ascites developed, similar periods recurred, and the condition became more severe during the following year. Autopsy revealed chronic passive congestion of all organs, anasarca, pleural effusion, dilatation of the heart, coronary sclerosis and an old infarct.

*Combined Type*—In a Negro the onset of the condition occurred at the age of 54, with cardiac decompensation, namely, edema of the ankles, enlarged heart, dyspnea and cyanosis. The condition improved under treatment. A few months later typical angina developed, with recovery. The patient died suddenly about a year after the onset of illness. Autopsy revealed old and recent cardiac infarction.

The causes of death in each of these groups are indicated in table 4.

The three remaining patients in the cardiac group died within three hours or sooner after admission. No histories could be obtained. The deaths were cardiac in type. No diagnoses were made. All three cases presented recent cardiac infarction at autopsy.

Twenty-three of the deaths in the cardiac group were due to recent cardiac infarction. The incidence of the latter condition was relatively higher in the anginal and dyspneic subgroups than in the congestive or combined groups. In fourteen of the twenty-three cases a clinical diag-

nosis of recent cardiac infarction was made. In the nine cases in which no diagnosis was made, three patients were in the hospital too short a period. In four others congestive failure obscured the sudden onset of increased dyspnea and cardiac collapse. In the two remaining cases no suggestive data in the histories or physical examinations suggested the diagnosis. One occurred in a man, aged 67, with diabetes and a history showing an anginal tendency, who, however, entered the hospital because of empyema. He was in a dying condition for a period of four days. Autopsy showed empyema and recent cardiac infarction. The other case occurred in a man, aged 60, with hemiplegia and motor aphasia and no antecedent cardiac history. Symptoms and signs of pneumonia developed, and the patient died within two weeks. Autopsy showed rheumatic endocarditis, mesenteric thrombosis, recent cardiac infarction and bronchopneumonia.

TABLE 4—*Causes of Death in Each Group of Cases*

	Number of Cases	Cause of Death	Number of Cases
(a) Anginal	11	Recent cardiac infarction	7
		Acute infections	3
		Cerebral thrombosis	1
(b) Dyspneic	12	Recent cardiac infarction	6
		Acute infections	2
		Pulmonary thrombosis	1
		Cerebral hemorrhage	1
		Undetermined by autopsy	2
(c) Congestive failure	14	Recent cardiac infarction	3
		Congestive failure	6
		Pulmonary thrombosis	2
		Acute infections	3
(d) Combined	16	Recent cardiac infarction	4
		Congestive failure	4
		Acute infections	5
		Pulmonary thrombosis	2
		Undetermined by autopsy	1

There were forty-four cases in the noncardiac group. In these cases the clinical syndrome involved primarily some other organ, and there was no indication of any cardiac lesion except as a terminal event in a few. It is interesting to note that nineteen of these forty-four cases presented the picture of a neurologic condition.

Nine of the deaths in the noncardiac group were due to recent cardiac infarction. In five of these cases the clinical picture was clear enough to warrant its diagnosis. The remaining four cases are mentioned briefly. In a patient with a neurologic condition, signs and symptoms of pneumonia developed, and autopsy revealed cardiac infarction. A second patient with a neurologic condition, bedridden, died suddenly without preceding symptoms of cardiac disease. A third patient, aged 83, with recurrent urinary retention, suddenly became irrational, and an irregular pulse rate and profuse perspiration developed. Death occurred



three days later, a diagnosis of uremia being made. In the fourth patient with a hernia of long standing abdominal pain and vomiting developed three days before death. The clinical diagnosis was strangulation of hernia. Autopsy showed recent cardiac infarction and no strangulation.

Of the patients with fibrosis interpreted as a result of old cardiac infarction, the large majority gave no clinical history suggesting previous acute infarction. The symptom of precordial pain was absent frequently.

In all, there were twelve sudden deaths, eight due to recent cardiac infarction, one to pulmonary thrombosis and one to pulmonary hemorrhage in tuberculosis and two in which autopsy failed to reveal the cause of the sudden death. Both of the latter cases were acute infections, one subacute bacterial endocarditis and the other acute ascending cholangitis.

#### SUMMARY

A series of one hundred autopsies showing myocardial infarction or gross myocardial fibrosis, constituting 10.6 per cent of nine hundred and forty-two autopsies performed, are analyzed. Thirty-two of these cases showed definite recent cardiac infarction while sixty-eight showed fibrotic patches, interpreted as probable old infarctions. Eighty-three were in males, seventeen in females. The average age of all patients was 60.8 years. The youngest was 28, the oldest 83. The average weight of the heart was 519 Gm. Most of the lesions were located in the left ventricular wall or involved the left ventricle and interventricular septum, but in fourteen cases the lesions were confined to the septum alone. Approximately 83 per cent showed moderate to marked coronary sclerosis. Coronary thrombosis was noted in twenty-four cases, in three there was thrombosis of both the left and the right coronary artery. Mural thrombosis occurred in thirty-four cases, in sixteen of which there had been recent infarction. Aneurysm of the left ventricle was noted in five cases, chronic adhesive pericarditis occurred in ten. Ten patients had positive Wassermann reactions while nine others showed evidence of vascular syphilis at autopsy. Hypertension occurred in approximately 60 per cent of the cases. In twenty-four cases in which electrocardiograms were taken, the most frequent change was abnormality of the T wave which occurred in twenty-three. Seventeen cases showed abnormalities of the Q-R-S complex, five auricular fibrillation and one complete heart block. Fifty-six cases presented cardiac symptomatology, while in the remaining forty-four the symptoms were referred to some other organ. Eight of the twelve sudden deaths in the series were due to recent cardiac infarction.

## CONCLUSIONS

1 Recent cardiac infarction and coarse myocardial fibrosis interpreted as healed infarction are extremely common observations at autopsy. They are usually associated with coronary sclerosis and cardiac hypertrophy.

2 Males are more frequently affected than females, the proportion is 5:1.

3 The average age is approximately 60 years, but there is a very wide variation.

4 Hypertension is present in approximately 60 per cent of the cases.

5 Only slightly more than one half of the patients presented clinical features of cardiac disease.

6 Change in the T wave and Q-R-S complex are the most frequent electrocardiographic abnormalities.

7 Patients presenting anginal or dyspneic syndromes are more prone to death from acute cardiac infarction than those with the congestive or combined type.

8 Of the noncardiac cases, approximately 20 per cent terminate with recent cardiac infarction. In approximately one half of the latter cardiac symptoms develop as a terminal event.

9 In the large majority of cases with coarse fibrosis interpreted as healed infarction there is no history of a previous cardiac accident.

# BISMUTH DIURESIS AND THE BLOOD AND URINARY CHANGES UNDER CLINICAL CONDITIONS

A B STOCKTON, M D

SAN FRANCISCO

The efficiency of sodium bismuth tartrate as a clinical diuretic and antiedemic has been sufficiently demonstrated in previous studies<sup>1</sup> It appeared desirable to throw light, if possible, on the mechanism of these actions It was especially desired to ascertain if the tissues in general might be the seat of the bismuth action This was tried by attempts to correlate the changes in the metabolites, especially the chlorides of the blood and urine, with the diuretic action Such an attempt on healthy rabbits indicated a tissue action of the bismuth<sup>2</sup> The same was found to be true not only for bismuth, but also for theophylline, and possibly digitalis, in human subjects discussed in a preliminary report<sup>3</sup> This paper presents various data and details of the results in patients with and without edema receiving bismuth

## METHODS

The results with bismuth were obtained in a total of fifteen different patients, six patients were used twice, thus making a total of twenty-one observations Of the fifteen patients, two (nos 15 and 16) were normal as far as their cardiovascular systems were concerned Three (nos 8, 12 and 13) of the remaining thirteen patients suffered from portal cirrhosis and ascites, and nine (nos 1, 2, 3, 4, 6, 7, 9, 10 and 11) had variable degrees of cardiac decompensation with edema, one patient (no 5) had anasarca associated with degenerative Bright's disease

The patients were kept at complete rest in bed throughout the period of observation, including the control periods without medication When the output of urine remained at a constant level, the bismuth

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Supported, in part, by a grant from the Rockefeller Fluid Research Fund of the School of Medicine, Stanford University

1 Hanzlik, P J , Bloomfield, A L , Stockton, A B , and Wood, D A Diuresis from Water-Soluble Bismuth, *J A M A* **92** 1413 (April 27) 1929  
Stockton, A B *Proc Soc Exper Biol & Med* **27** 721, 1930, *Arch internat de pharmacodyn et de therapie* **41** 52, 1931

2 Stockton (footnote 1, third reference)

3 Stockton (footnote 1, second reference)

was injected. A constant intake of fluid and of sodium chloride was maintained throughout. Complete daily twenty-four hour specimens of urine were collected and analyzed. Samples of venous blood were obtained at the same time each day. The urea of the blood and urine was estimated in five patients (nos. 3, 4, 6, 9 and 11), Folin's aeration method being used,<sup>4</sup> the estimations were not extended to the remaining patients because the significance of the changes, for the purpose of the work, was not clear. The chloride of the blood was estimated by Austin and Van Slyke's method,<sup>5</sup> and the chloride of the urine, by the method of Seelman and Volhard,<sup>6</sup> in all but four patients (nos. 1, 5, 7 and 10). The hemoglobin of the blood was estimated in ten patients (nos. 2, 3, 4, 5, 6, 8, 9, 10, 11 and 12), Palmer's method<sup>7</sup> being used. The object of this was to see if changes in the blood volume occurred, but as there were no constant or significant changes demonstrable, the data are omitted. The negative character of these results indicates that the changes in the blood metabolites to be discussed were not the result of changes in the blood volume.

The individual daily changes in the output of water and the chlorides and urea of the blood and urine for the various patients are presented graphically in chart 1. Chart 2 indicates the percentage of change in the different subjects.

In most of the patients, the bismuth was used following the administration of various other diuretics as follows: in patients 3, 7 and 16, after a full course of medication with digitalis, in patients 4, 6, 9 and 10, after digitalis and theophylline, in patient 1, after digitalis, theobromine and theophylline ethylenediamine, in patient 11, after digitalis, theophylline, theobromine, sodiosalicylate and mersalyl, in patient 13, after mersalyl and ammonium chloride, and in patient 12, after mersalyl and merbaphen. Only patients 5, 8, 15 and 16 were given bismuth sodium tartrate as the initial diuretic. In other words, the majority, or eleven patients, received the bismuth under unfavorable conditions, that is, after all other medication had failed. In these patients, there was an opportunity for the comparison of bismuth with the more common diuretics. The comparative efficiency of the various diuretics will be considered in a separate paper.

It is seen from the individual data in chart 1 that fourteen of eighteen trials with bismuth in fifteen patients showed a definite diuretic action. Four patients (nos. 4, 10, 12 [second injection] and 13) showed no, or only a slight, increase in diuresis. There was a marked diuresis in ten of the fifteen patients (nos. 2, 3, 5, 6 [first injection], 7, 8, 9,

4 Folin, O. *Ztschr. f. physiol. Chem.* **32** 504, 1901.

5 Austin, J. H., and Van Slyke, D. D. *J. Biol. Chem.* **40** 345, 1930.

6 Seelman, J. J. *J. Lab. & Clin. Med.* **1** 444, 1916.

7 Palmer, W. W. *Proc. Soc. Exper. Biol. & Med.* **12** 175, 1914.

11, 12 and 16) Three patients (nos 6, 7 and 13) showed diuresis after one injection of bismuth, and not after a preceding or subsequent injection. This phenomenon was observed not only with bismuth, but also with the other diuretics. Most patients responded to the first diuretic agent with an increased output of urine, but failed to respond to the second diuretic agent unless an interval of from two to seven days had elapsed between the two administrations. In general, therefore, the usual peculiarities attendant on the actions of diuretics were evident also in the action of bismuth, although the bismuth in the patients here reported acted at a disadvantage in all but four, since it was used only after other diuretics had been tried.

The efficiency of the diuretic action of bismuth, as indicated by the maximum and median percentage changes in the output of urine, is

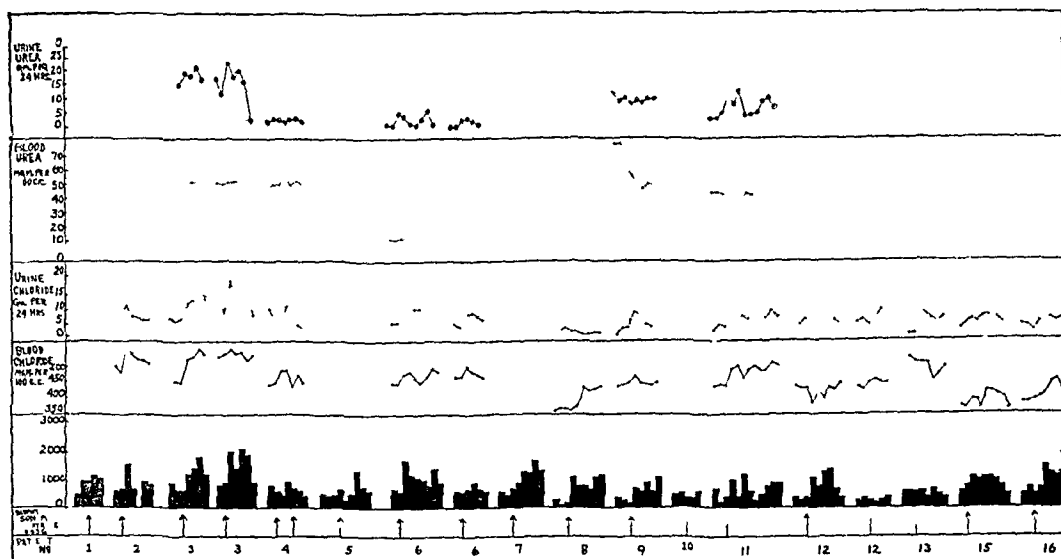


Chart 1—Diuresis and changes in the chloride and urea of the blood and urine of edematous and normal patients after the intramuscular injection of bismuth sodium tartrate. Each arrow represents a total dose of 0.03 Gm. of the bismuth compound, or 0.022 Gm. of bismuth ion.

shown in chart 2, which also illustrates an attempted correlation with the total fluid removed from the body. The maximum percentage diuresis would indicate the most that might be expected from the bismuth and was obtained by comparing the mean daily output of urine with the peak of daily output after the injection of bismuth. The total fluid removed represented the volume of urine excreted after the administration of bismuth in excess of the mean control level of urine during equal periods of four days.

It is seen that the maximum percentage of diuresis in all patients ranged from minus 18 to plus 360, average, plus 127. The percentage change in the total diuresis as indicated by the difference between the

volume of urine excreted during three days before and three days after the injection of bismuth ranged between minus 48 and plus 228, average, plus 56. Accordingly, both methods of estimating the diuretic efficiency of the bismuth showed a definite and considerable increase in the output of urine. In fact, the data for the percentage of total diuresis testify to the well sustained diuretic action of the bismuth.

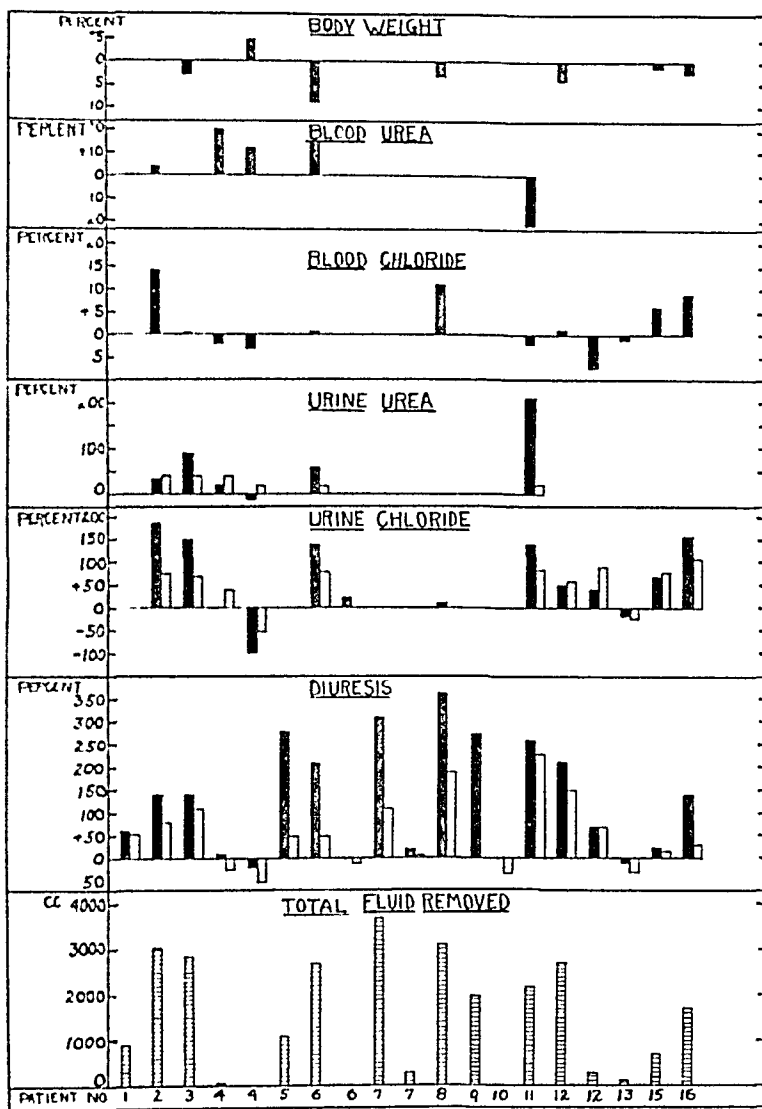


Chart 2—Total fluid removed and percentage changes in the output of urine, body weight and blood and urine chloride and urea following the injection of bismuth sodium tartrate in edematous patients. The solid blocks represent maximum percentage changes, the hollow blocks, the median change during the four days preceding and the four days following the injection of bismuth.

and the absence of secondary oliguria as compared with merbaphen and mersalyl.<sup>1</sup>

#### CHANGES IN THE CHLORIDE

*Urine*—In eight of the eleven patients studied, the excretion of chloride in the urine increased following the injection of bismuth, the

increase failed only in patients 4, 8 and 13. In patients 4 and 13 the absence of an increase in the excretion of chloride correlated with a failure to respond with an increase in diuresis. In patient 8, the chloride in the urine failed to increase despite a brisk diuresis. On the other hand, patient 6 (second injection), who failed to show an increase in diuresis, and patient 12 (second injection), who showed a doubtful increase, exhibited definite increases in the excretion of urinary chloride amounting to 28.3 and 87.8 per cent, respectively. In seven of eleven patients, there was an increase in the concentration of chloride in the urine independent of the volume of the urine, the concentration of the urinary chloride ranged from minus 70 to plus 70 per cent, average, minus 11 per cent. The variations in the concentrations were too great to indicate their significance, the outstanding item being an absolute daily increase in the urinary chloride.

The percentage changes in the daily excretion of urinary chloride in the urine are shown in chart 2, the changes were plotted in the same way as those for diuresis. It is seen that the maximum excretion of chloride varied from minus 16 to plus 154 per cent, average, plus 67 per cent. The percentage of the total excretion of chloride ranged from minus 50 to plus 110, average, plus 54.7. Thus, the changes in the chloride were in the same general direction as those in the diuresis, but the magnitude of the increases was less, i. e., about one-half. Accordingly, the increase in the output of urine would account for the increased excretion of chloride.

*Blood*—The changes in the chloride closely paralleled the changes in diuresis and in urinary chloride, thus pointing to the tissues as the source of extra chloride. An active diuresis following the injection of bismuth was always accompanied by an increase of chloride in the blood, and a decrease or absence of diuresis was accompanied by no change or a decrease of chloride in the blood in three patients (nos. 4, 12 and 13). The changes in the chloride of the blood in the eleven patients observed ranged from minus 7 to plus 14 per cent, average, plus 2.6 per cent.

#### CHANGES IN THE UREA

*Urine*—In six of nine trials with bismuth in the five patients studied, there was a concurrent increase in the excretion of urea with water. One patient (no. 9) showed a decrease, and one patient (no. 4, both trials), no change in excretion. These two patients, who showed no increase of urea in the urine, showed no increase in diuresis. The increases in the average total excretion of urea per day ranged from 14 to 40 per cent, average, 27 per cent, these changes are shown in chart 2. There was also a definite increase in the concentration of urea in the urine of all patients, the daily increases ranging from 5 to 56 per

cent, average, 32 per cent. From these results, it would seem that the increases in the output of urea in the urine were due to the increase in diuresis.

*Blood*—The urea in the blood following the use of the bismuth showed no change in six trials in four different patients (nos 3, 4, 6 and 11) and a decrease in one patient (no 9). In the latter patient, who had cardiac decompensation, the fall in urea in the blood occurred with the onset of clinical improvement, loss of edema and recovery of the circulation. The urea in the blood of all the patients studied varied from minus 22 to plus 20 per cent, average, plus 5 per cent, all of which testifies to the considerable variation without a significant net change. This might be expected, since the distribution of urea in the body is kept fairly constant and the balance is not easily upset.

#### CHANGES IN BODY WEIGHT

In all edematous patients who showed an active diuresis, the loss in body weight was marked. Unfortunately, not all of the patients used could be weighed daily. All of the seven patients who could be weighed lost body fluid following the use of the bismuth, except one (no 4), in whom diuresis failed to occur. The percentage changes in the body weight in these patients ranged from a gain of 7.4 to a loss of 9.5, the average being a loss of 2.7. The gain in weight occurred in patient 4. The amounts of edema fluid removed during periods of diuresis ranged from 0 to 3,860 cc, an average of 1,448 cc (chart 2).

#### COMMENT

Taking the results obtained as a whole, it was found that bismuth sodium tartrate caused diuretic and antiedemic actions in about 73 per cent of the edematous patients observed. The diuresis began in from twenty-four to forty-eight hours after intramuscular injection of the bismuth, and persisted for from two to eight days. The average duration of diuresis was four days, when the output of urine remained at an average of about 56 per cent higher than before the injection of bismuth. The period of maximum diuresis usually fell on the first to the third day following the administration of the bismuth, and at this time the output of urine averaged 122 per cent above the control level. The edema fluid was removed at a slower rate than with other diuretics, such as theophylline, merbaphen and merxalyl, but since the bismuth diuresis continued for several days, the bismuth eventually removed more fluid than the other diuretics.

The most significant changes for the mechanism of the bismuth action were the simultaneous increases in the chlorides of the blood and urine during the increase in diuresis. This correlation is good



evidence in support of a general tissue action of the bismuth, an action in common with that of some other recently studied diuretic agents, namely, theophylline and the organic mercurials, merbaphen and meisalyl. Since the increase in salt of the blood must come from the tissues, the mechanism of the diuretic action, and of the antiedemic action as well, would appear to be essentially a salt action, dependent on a mobilization of the salt in the tissues. Since the increase of chloride in the blood was frequently manifested before the diuretic action, this phenomenon pointed to the tissues as the seat of action of the bismuth. This, however, does not exclude the possibility of the water being removed first from the tissues into the blood. It is possible that both the salt and the water are removed together. Inhibition or paralysis of reabsorption in the renal tubules is not adequate to explain the simultaneous increases in the chloride of the blood and urine. There would seem to be no alternative to some tissue action of the bismuth in order to account adequately for the increased output of sodium chloride in the urine when the chloride in the blood is elevated during the diuresis. These changes in the chloride of the blood and urine of patients agree closely with those in the chloride of the blood and urine of rabbits treated with bismuth.<sup>2</sup>

It has been previously reported, and was constantly observed in the patients of this study, that the chloride in the blood was lower in edematous patients than in normal subjects. This not only would agree with the common view that salt is retained in tissues during edema and account for the low blood salt, but also would point to the tissues as the source of the chloride mobilized by diuretics such as bismuth.

The urea of the body cannot assist satisfactorily in locating the seat of action of diuretics, because any changes in the urea in the blood are quickly adjusted and the concentration is kept constant. The increase in daily urea of the urine might be used as an argument in support of a renal action for the bismuth, i. e., a result indicating inhibition or paralysis of, or injury to, tubular reabsorption. However, a tissue action could not be denied, despite the failure to demonstrate an increase in urea in the blood, which is not practically demonstrable for the reason stated. It is believed that changes in other metabolites that more satisfactorily reflect a direct tissue action should be studied before a general tissue action for various diuretics is finally accepted. Such studies are now being attempted with bismuth. For the present, at least, the chemical evidence points to a tissue action as an important factor in the diuretic action of bismuth and probably also of the organic mercurials and the puines. This evidence does not deny a renal factor in the diuretic action, in fact, the kidney would share the general tissue action. The relative importance of these two factors in the action of diuretics cannot yet be precisely defined.

As for the practical advantages in the choice of bismuth as a diuretic and antiedemic, the following may be stated. Well sustained diuresis, lasting from five to six days, results in the removal of large quantities of fluid, there is an absence of nausea and vomiting, which are frequently caused by theophylline, there is much less danger of metallic poisoning (stomatitis) and renal injury than when merbaphen and mersalyl are used, intramuscular injection avoids the objectionable features of venous injection, which is sometimes resorted to when other diuretics are used, and of oral administration, which, when used for other diuretics, is disturbing to digestion. About the only disadvantage of the use of bismuth is a slower onset of action, bismuth is not as spectacular as are merbaphen and mersalyl. However, this disadvantage is offset by the advantages cited. There is a certain variability in the action of bismuth, but this is also true of all diuretics.

#### CONCLUSIONS

1 The intramuscular injection of bismuth sodium tartrate into fifteen patients was followed by a definite and sustained increase in diuresis in 73 per cent. The increase in the output of urine correlated with the losses of edema fluid and of body weight in the edematous patients.

2 In the four patients who failed to respond, there was no diuretic action following the use of various other diuretics.

3 In the patients studied, the urea in the blood showed no constant or significant changes, while the urea in the urine generally paralleled the changes in diuresis.

4 The chloride of the blood and urine increased simultaneously during increases in diuresis in the majority, or eight, of the eleven patients studied, thus indicating that the diuretic action of bismuth is mediated through some effect of the metal on the tissues.

5 This correlation of the changes in the chloride of the blood and urine and the diuresis in human subjects agrees with that in rabbits receiving bismuth.<sup>2</sup> The tissue action suggested for bismuth agrees also with that suggested by other investigators for other diuretic agents (merbaphen, mersalyl and theophylline). Various other factors in diuretic actions are discussed.

# EXPERIMENTAL LOW COLONIC OBSTRUCTION

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Recent experimental work has emphasized the importance of chloride metabolism in high intestinal obstruction and has offered much of value in the treatment for this condition. Relatively few studies have been made on obstruction low in the large bowel, which produces a somewhat different though not fundamentally dissimilar syndrome. It was felt that a careful study of low obstruction might supplement our knowledge of intestinal obstruction in general by bringing out similarities and differences between low and high obstruction, and might possibly yield information of practical importance for therapy.

McClure,<sup>1</sup> in 1907, produced colonic obstruction by ligation with a cotton cord. Vomiting was prominent, although no food or drink was taken postoperatively. The animals were very drowsy, and the symptoms were progressive, the average length of life was seven days. Dilatation just above the ligature was often enormous, and was uniform up to the ileocecal valve, above which the small intestine gradually tapered to normal size. Brandberg<sup>2</sup> stated that animals with obstruction of the large intestine live longer than those in which the obstruction is in the small intestine, that the cause of death is peritonitis due to gangrene of the colon, and that there are no changes in the blood except those associated with starvation. Wangenstein and Chunn<sup>3</sup> reported that one dog lived forty-two days with complete obstruction low in the descending colon, the blood nonprotein nitrogen in this animal did not increase. Excretion of nitrogen in the urine was increased. At autopsy

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1 McClure, R D. An Experimental Study of Intestinal Obstruction, *J A M A* **49** 1003 (Sept 21) 1907

2 Brandberg, R. Experimental and Clinical Study of Chemical Blood Changes in Ileus, *Acta chir Scandinav* **65** 415, 1929, abstr, *J A M A* **95** 311 (July 26) 1929

3 Wangenstein, O H, and Chunn, S S. Studies in Intestinal Obstruction. III. Simple Obstruction. Study of Cause of Death in Mechanical Obstruction of Upper Part of Intestine, *Arch Surg* **16** 1242 (June) 1928

the entire colon was packed with solid fecal material. Wangensteen stated that the administration of saline solution is of no benefit in such animals.<sup>4</sup>

Several workers<sup>5</sup> have reported on obstruction just above the ileocecal valve, the symptomatology of which is midway between that of high intestinal and that of low colonic obstruction. In such animals vomiting occurs later and is less abundant than is the case in high obstruction, the length of life is longer, the change in the blood chlorides takes place more slowly, and the increase in urea nitrogen is a less prominent part of the picture. In this type of obstruction the subcutaneous administration of sodium chloride is reported to be of some benefit. The picture produced by an obstruction high in the small intestine need hardly be reviewed. It may be recalled, however, that unless chloride is administered death occurs rapidly, with an equally rapid fall in blood chloride and a rise in nonprotein nitrogen. If chloride is given the animal may be maintained in a fairly normal state for several days.<sup>6</sup>

#### METHOD

The effects of obstruction of the colon were studied in sixteen dogs, animals dying of pneumonia and perforative peritonitis not being included. In eleven the obstruction was brought about by tying off the descending colon a few inches from the anus with a gauze band. This is a satisfactory method of producing the obstruction, except that the animals must be carefully watched, because they may begin to defecate small amounts after several days. In three of the eleven animals the ligature "slipped" in this way, leaving an opening large enough to admit a small probe. The results in these three animals will be compared with those in the sixteen in which obstruction was complete. In five dogs obstruction was produced by sectioning the descending colon in the same region and inverting the ends with sutures. All surgical procedures were carried out with aseptic technic, pentobarbital sodium or ether being used as the anesthetic.

The plasma chlorides, blood urea, hemoglobin, red cell count, total volume of the blood and blood indican were studied in dogs before and after complete obstruction of the distal descending colon. In addition, several animals received barium enemas just prior to operation, and the position of the barium was observed postoperatively by fluoroscopy and roentgenograms. A careful autopsy was performed in every case.

Plasma chlorides were determined by the method of Rapple, and blood urea nitrogen was measured by the Folin-Wu technic. The total volume of the blood was determined by the Rountree method, as modified by Hooper, Smith,

4 Wangensteen, O. H. *Minnesota Med* **14** 16, 1931.

5 Haden, R. L., and Orr, T. G. *J. Exper. Med.* **37** 365, 1923. Hartwell, J. A., Hoguet, J. P., and Beekman, F. An Experimental Study of Intestinal Obstruction, *Arch. Int. Med.* **13** 701 (May) 1914.

6 Haden, R. L., and Orr, T. G. Obstruction of the Jejunum, Effect of Sodium Chloride on Chemical Changes in the Blood of the Dog, *Arch. Surg.* **11** 859 (Dec.) 1925.

7 Rapple, W. C. *J. Biol. Chem.* **32** 509, 1918.

Belt and Whipple,<sup>8</sup> using vital red Determinations of blood volume were not repeated more often than every three days, to avoid accumulation of dye in the blood stream Semiquantitative determinations of blood indican were made by the method of Monias and Shapiro,<sup>9</sup> it was our original intention to perform quantitative studies of blood indican as an index of impairment<sup>9</sup> of the kidney if the findings warranted this, but the only animals in which the blood indican was definitely increased were those in which peritonitis was present as a result of perforation

#### RESULTS

In a number of the dogs not included in our series of sixteen, death was due either to pneumonia or to perforation of the large bowel Perforation usually took place a few inches above the site of obstruction These dogs were excluded from the series, because we were interested only in the changes produced by simple obstruction of the colon and not in those caused by a complicating peritonitis In thirteen dogs no cause of death other than the obstruction could be found The average length of life of these animals was ten and two-tenths days, with a minimum of six and a maximum of twenty-two days There was no definite difference in the span of life in the dogs in which the obstruction was caused by ligature and those in which the intestine was severed and the ends were inverted When perforation resulted, it was found to occur at any time from the second to the ninth day Autopsy observations in the animals dying of simple obstruction were a greatly dilated large intestine, usually hyperemic on the antimesenteric border but not discolored, a small bowel dilated from one-third to three-fifths of its extent but not hyperemic, a stomach containing considerable amounts of fecal material, and a markedly distended gallbladder The contents of the small and large bowel were invariably fluid as contrasted with the solid content reported by Wangensteen<sup>4</sup> The peritoneum was everywhere smooth and glistening, with no excess fluid in the peritoneal cavity

The animals as a rule ate and drank freely for the first few post-operative days Water was consumed in moderate amounts by most of the dogs until a few hours prior to death The appetite gradually decreased, and vomiting of small amounts of material usually began from about the fourth to the sixth day, although the onset of vomiting varied considerably In the animals that lived longest the vomitus became fecal Progressive cachexia invariably occurred, and drowsiness was marked, the animals appeared to be dehydrated

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<sup>8</sup> Hooper, C W , Smith, H E , Belt, A E , and Whipple, G W *Am J Physiol* **51** 205, 1920

<sup>9</sup> Monias, B L , and Shapiro, P Value of Indican Determination in Blood in Cases of Renal Insufficiency, *Arch Int Med* **45** 573 (April) 1930

The plasma chlorides were determined in twelve dogs and the results are summarized in table 1. No significant change in chloride took place even in the dogs that lived nineteen and twenty-two days.

Determinations of the blood urea nitrogen were made in nine animals. All showed a gradual rise. In two instances samples of blood for deter-

TABLE 1—*Plasma Chlorides After Obstruction*

Day Postoperative	Dog											
	1	2	3	4	5	6	7	8	9	10	11	12
Normal	460	500	525	590	550	560	525	595	572	573	564	565
1	480	510	543	593		540						
2	478	548	523				572					
3	461	460	520		560			585	498			
4	412	533	540				595	595				
5	338	521	448	598	561	553	556				491	
6		540	485				511	585	445	522	565	
7				540	500	580						570
8							523	590			510	
9												
10								540				
11							535				519	
12							486	562			520	506
13							500	585			544	
14							520					
15							495	600				
16												
17							500	555				
18												
19							525	582				
20							531					

TABLE 2—*Urea Nitrogen After Obstruction*

Day Postoperative	Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6	Dog 7	Dog 8	Dog 9
Normal	9.2	12.7	11	12	9.6	9.7	17	13	14.6
1									
2									
3				13		13			
4				10			70		
5	12	20.4	17			12.5		24	18
6		21.6		16.4	14				
7	19.8					18.1			
8		22.5	65			21			
9									
10		22							
11	12								
12	14.7	22							
13	14.3								
14	14	23							
15	18.3	29							
16		32							
17	24.3	35							
18		45							
19	28.6								
20	28.8								

mination of urea were drawn from the heart a few minutes prior to death, these determinations gave sixty-five and seventy mg of urea nitrogen, respectively, per hundred cubic centimeters. In both of these animals there was no cause for death other than the obstruction. These results are shown in detail in table 2.

Red blood cell counts, hemoglobin and determinations of blood volume were made on six animals. The red blood cell count and hemo-

globin showed little change. In four of the six dogs, however, the blood volume definitely decreased. The figures are given in table 3. The changes in blood volume are strikingly illustrated by dog 5, which began to defecate small amounts on the seventh day, in this animal the blood volume first decreased thirty-eight per cent, and then, after the obstruction was partly relieved, it rose above its normal level.

Semiquantitative tests for blood indican were made on eight dogs. The amount of indican increased very slightly above the level shown by normal controls, according to Monias and Shapiro,<sup>9</sup> the maximum amount present was not sufficient to indicate impairment of the kidneys.

Although the fecal vomiting observed would seem to indicate regurgitation from the lower part of the bowel, it seemed important to show

TABLE 3—*Hemoglobin, Red Blood Cell Count and Blood Volume After Obstruction*

Number of Dog	Day Post Operation	Hemoglobin per Cent	Red Blood Cell Count	Length of Life, Days	Blood Volume, Cc	Comment
1	Normal 4	110	7,440,000	6	1,660	
		120	8,640,000		1,770	
2*	Normal 3	100	6,350,000	5	1,469	
		100	6,400,000		1,344	
3	Normal 3 7 11	101	6,750,000	12	1,622	
		101	6,320,000		1,397	
		105	6,810,000		1,289	
		95	6,720,000		1,009	
4	Normal 5 8	102	7,660,000		1,131	Ligature slipped on seventh day
		106	6,920,000		697	
		102	7,330,000		1,476	
5	Normal 4	95	6,650,000	6	1,681	
		97	7,170,000		1,007	
6	Normal 4	104	7,550,000	8	1,495	
		105	7,830,000		992	

\* This dog died of peritonitis secondary to perforation two days after the second determination of blood volume.

conclusively that this occurred because passage of colonic contents to the small intestine, where they might be more readily absorbed, could be a factor in the production of toxemia. The fecal character of the vomitus could result from the extension of colonic flora into the gastrointestinal tract. Fluoroscopy and roentgenograms showed that barium placed in the colon by enema before operation gradually moved up into the small intestine. Barium was not observed to reach the stomach, probably because dilution by fluid in the upper part of the small intestine reduced the concentration of barium to a point where no shadow was cast. In a preliminary report<sup>10</sup> we stated that the barium placed in the colon was not seen to pass back past the ileocecal valve. At

10 Roberts, G. M., and Crandall, L. A. Jr. Proc. Soc. Exper. Biol. & Med. 28: 942, 1931.

this time we were following the position of the barium by fluoroscopy only, more recently roentgenograms have shown definitely that the barium is regurgitated into the small bowel

It is interesting to compare the results in the dogs in which the obstruction was relieved by loosening of the ligature with those in the animals in which the intestinal closure was permanent. The return to a normal blood volume in dog 4 (table 3) has already been noted. In the other two animals in which this occurred only the plasma chloride was determined, in two dogs the chlorides showed a tendency to fall, even though the animals passed small amounts of liquid feces and their general condition improved. It was striking to see the change from a listless state to more nearly normal vigor in these animals after the passage of small amounts per rectum for a few days. Two dogs with an intentional partial obstruction were observed by one of us (Dr. Crandall), although chemical examination of the blood was not made. These animals lost weight, but showed almost normal spontaneous activity. Death occurred after four and five weeks, and was due to a complete obstruction caused by a mat of hair and feces lodged at the site of ligation. Intestinal distention in these animals was enormous.

#### COMMENT

It is to be noted that while the period of survival of some of our animals approached that of animals subjected to simple starvation, the majority died in from six to twelve days. Loss of chlorides is evidently a factor of slight, if any, importance, changes in chloride metabolism are further eliminated by the observation of Wangenstein and Chunn that administration of chlorides is of no benefit in these animals. The picture presented is that of toxemia. The obvious factors to be considered are dehydration, injury to the kidney and absorption of some unknown toxin from the bowel.

The presence of renal damage might be inferred from the rise in blood urea nitrogen, but the slight change in blood indican contradicts such a supposition. The situation is in all probability similar to that occurring in high obstruction, in which the increase in blood urea nitrogen is not accompanied by an increase in the other fractions of the nonprotein nitrogen. Several workers have indicated that while some renal impairment is present in high obstruction, it is probably not sufficient to account for the death of the animals.<sup>11</sup>

The dehydration that occurs is severe. Three of our animals lost 30, 40 and 33 per cent of their blood volume respectively these losses

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11 Cooper, H. S. F. Cause of Death in High Obstruction, *Arch. Surg.* **17** 918 (Dec.) 1928. McQuarrie, I. and Whipple, G. H. *J. Exper. Med.* **29** 397, 1919.



being present one, two and four days before death. A fourth animal lost 38 per cent of its blood volume, but then began to defecate small amounts and recovered. Of the remaining two dogs, one had lost about 8 per cent of the blood volume and the other showed an increase of 7 per cent, readings in both cases being made two days before death. Owing to technical difficulties in making repeated determinations, we have not been able to determine the blood volume at as short intervals as would be desirable, and we realize that the dehydration may be sufficient in the last hours of life to be of itself a cause of death. The cause of the dehydration is obscure. No large amounts of fluid were lost by vomiting in any case, nor was the amount in the bowel large enough to account for the loss of fluid when it is considered that the animals took water by mouth voluntarily up to a short time before death. The relative constancy of the red cell count and the determinations of hemoglobin in the face of the decreasing blood volume show that the former factors cannot be relied on to give an index of blood concentration. The findings can be interpreted only as a storage or a destruction of red cells.

We believe that our studies indicate that in low obstruction some toxic material is absorbed from the intestine which is responsible for the fatal issue. We have no crucial evidence to present on this point, such a deduction is purely a matter of elimination. The toxic substance must also be responsible for the decrease in the blood volume. Those who have studied high obstruction are divided in opinion, some believing that the sole cause of death is the loss of fluid and salts,<sup>12</sup> others presenting evidence that a distended mucosa may absorb such toxic substances.<sup>13</sup> In low obstruction the issue seems somewhat clarified, there is no rapid loss of chloride to obscure the picture, and there is no extremely rapid piling up of nonprotein nitrogen. For the first few days the animals appear essentially normal. It may well be that symptoms from such an obstruction do not begin to appear until the entire colon is distended to its maximum capacity and material begins to accumulate in the lower part of the small bowel. Dragstedt, Lang and Millet<sup>14</sup> have presented reasons for believing that the colon is less

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12 White, J. C., and Fender, F. A. Cause of Death in Uncomplicated High Intestinal Obstruction, *Arch Surg* **20** 897 (June) 1930. Gamble, J. L., and Ross, S. G. *J Clin Investigation* **1** 403, 1925.

13 Dragstedt, L. R. *Proc Soc Exper Biol & Med* **25** 239, 1928. Dragstedt, L. R., Dragstedt, C. A., McClintock, J. T., and Chase, C. S. *J Exper Med* **30** 109, 1919.

14 Dragstedt, C. A., Lang, V. F., and Millet, R. F. Relative Effects of Distention on Different Portions of the Intestine, *Arch Surg* **18** 2257 (June) 1929.

susceptible to injury by distention than is the ileum, and the ileum less than the jejunum. We suggest that the immediate relief that follows even the smallest opening at the point of obstruction is an additional reason for believing that the primary factor is distention with an attendant change in the permeability of the intestinal mucosa.

#### CONCLUSIONS

1 In a series of animals subjected to two types of surgical obstruction of the descending colon, thirteen died from no apparent cause other than the obstruction. The average length of life was ten and two-tenths days, the maximum being twenty-two and the minimum six.

2 Such animals show no significant change in plasma chlorides at any time.

3 The blood urea nitrogen increases gradually, and in our series reached a maximum value of 70 mg per hundred cubic centimeters at the time of death.

4 A slight increase in blood indican was observed.

5 The red blood cell count and the hemoglobin show no definite change. There is a tendency for the blood volume to decrease sharply, the maximum loss observed being 40 per cent.

6 Regurgitation of barium from the colon into the small intestine has been demonstrated in these animals.

7 The possible causes of death are discussed.

# TOXICITY OF MERSALYL (SALYRGAN)

## A CLINICAL AND ANATOMIC STUDY

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Despite the widespread use of the newer mercurial diuretics, merbaphen (novasurol) and mersalyl (salyrgan), there still exists some doubt as to their ultimate harmlessness. Stomatitis, colitis, proctitis, purpura, hematuria and even death have been reported following the use of novasurol. With the introduction of salyrgan there was noted a decrease in the severity and number of the reactions <sup>1</sup>

In his experiences with both drugs, Petzal <sup>2</sup> called attention to the change. In several hundred injections of salyrgan he saw no toxic manifestations. At necropsy Agnew <sup>3</sup> observed hemorrhagic colitis in eight subjects following the use of novasurol, but no such manifestation occurred after the injection of salyrgan, despite its more extensive use at that time (1926). Beinheim <sup>4</sup> recorded the administration of 1,000 injections of salyrgan without complicating reactions. Tscherning <sup>5</sup> warned against the active use of the drug in aged men with complicating prostatic hypertrophy. In four of his patients there was a

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1 Zeiler, K. Novasurol, ein neues Quecksilbersalz zur Syphilisbehandlung, mit Bemerkungen ueber die Grundsätze der Quecksilberbehandlung, München med Wchnschr **44** 1257, 1917. Christian, H. A. Diuretics—Their Utility and Their Limitations, Boston M & S J **197** 614, 1927. Snell, A. M., and Rowntree, L. G. Purpuric Skin Manifestations Following the Use of Merbaphen, Ann Int Med **2** 97, 1928. Redlich, F. Letale Quecksilber Intoxication nach einmaliges Novasurol Injektion, Wien klin Wchnschr **38** 359, 1925. Gunsberg, M. Klinische Erfahrungen ueber Salyrgan, ein neues Diuretikum, Deutsche med Wchnschr **51** 604, 1925. Marvin, H. M. Merbaphen as a Diuretic in Congestive Heart Failure, J A M A **87** 1016 (Sept 25) 1926. Sprunt, D. H. Renal Damage Following Administration of Merbaphen, Arch Int Med **46** 494 (Sept) 1930.

2 Petzal. Erfahrungen mit Salyrgan, Deutsche med Wchnschr **52** 1651, 1926.

3 Agnew, G. H. Salyrgan as a Diuretic, Canad M A J **18** 45, 1928.

4 Beinheim, E. Ueber das neue Quecksilberpräparat, Salyrgan, als Diuretikum, Therap d Gegenw **65** 538, 1924.

5 Tscherning, R. Ueber Salyrgan, Deutsche med Wchnschr **53** 1465, 1927.

profuse diuresis followed by acute retention owing, probably, to prostatic swelling. Petri<sup>6</sup> recorded changes in the colon consisting of greenish-yellow, sparsely placed, superficial ulcerations which appeared after effective injections of novasurol and salyrgan.

Grossman,<sup>7</sup> reviewing his experience with nearly 10,000 injections of salyrgan, recalls no damage that he could directly attribute to the drug. Because the chemical structure of salyrgan is different from that of novasurol, he believes that its toxicity is not the same. He cites the history of two patients suffering from congestive heart failure with generalized edema and ascites, in whom the injection of from 0.5 to 1 cc of novasurol produced diuresis accompanied by hemorrhagic stomatitis and colitis. Salyrgan was equally effective as a diuretic but caused no complications. Grossman was able to continue the administration of the latter drug for months at a time, giving as many as three injections per week. Fishberg<sup>8</sup> speaks of the replacement of novasurol by salyrgan in the use of mercurial diuretics in the treatment of edema.

In a recent review of mercurial diuretics, Engel and Epstein<sup>9</sup> reported their own experience with several thousand injections of salyrgan. They regard the use of novasurol as obsolete. They can replace it with salyrgan and produce an equally effective diuresis, and they seldom see any complications due to mercurial intoxication.

During the past five years at the Montefiore Hospital when a mercurial diuretic was found necessary, only salyrgan was used. In more than 3,000 injections given to date, there have been only isolated instances of harmful reactions. To complete the clinical impression of the lesser toxicity of salyrgan as compared with other mercurial diuretics we have attempted a correlative study of the course of illness, the amount of drug administered and the anatomic findings in a group of thirty patients who were followed at the hospital for the past five years. They were as a rule patients with signs of severe congestive heart failure, who had been admitted to other institutions several times previously. They were observed and treated at the hospital until death. In all cases special search was made for signs of mercurialism in the kidney. The colon was investigated only in the gross, and in no case were signs of ulceration found.

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6 Petri, E, Vergiftungen, in Henke, F, and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1927.

7 Grossman, M. *Moderne Diuretika*, Schweiz med Wchnschr **58** 1249, 1928, Novasurol und Salyrgan, *Med Klin* **21** 1730, 1925.

8 Fishberg, A. *Hypertension and Nephritis*, Philadelphia, Lea & Febiger, 1930, p 101.

9 Engel, K, and Epstein, I. *Die Quecksilberdiurese*, *Ergebn d inn Med u Kinderh* **40** 187, 1931.

From a clinical point of view our patients showed only a negligible number of reactions attributable to mercury itself. In one patient a wrist-drop developed and two had foot-drop incidental to faulty intramuscular injections. In two patients with impaired renal function a mild stomatitis developed following a single injection of salyrgan.

Since the toxic action of mercury is both immediate and remote, we have included in our reports a group of patients to whom the salyrgan was given shortly before death, although the amount administered was small. Salyrgan was withheld only in those who showed severe renal damage, such as elevated amount of urea in the blood, hematuria, or a low fixed specific gravity of the urine. Albuminuria and casts were not contraindications. The total amounts of salyrgan given ranged from 4 to 130 cc.

Of all the patients investigated only one showed a renal lesion suggestive of mercurial intoxication. The protocol of the case follows.

#### REPORT OF A CASE

*History*—C. C., a pale Italian boy of 5 years, was admitted to the hospital on July 23, 1928, with a history referable to chronic rheumatic cardiovalvular disease for the past year. Throughout this period he showed slight rises in temperature, which might be interpreted as signs of rheumatic activity. When first seen he was acutely ill, with intense dyspnea and orthopnea. Cyanosis of the lips, ears and fingers was present. The veins of the neck were distended. The heart was markedly enlarged to the left and the right, with the apex beat 8 cm. to the left of the mid-sternal line and in the fifth interspace. The liver was palpable two fingers below the costal margin. There was no evidence of edema or ascites.

*Course*—During the first month the patient was afebrile, and after a short period of rest the dyspnea diminished, leaving him much more comfortable. On Aug. 26, 1928, acute pharyngitis with a rise in temperature to 104 F. developed. This lasted two days and the temperature then returned to normal. On September 13, nearly two weeks later, edema of the lower extremities and puffiness of the face were noted. The patient was intensely dyspneic as well. Following the administration of 4 cc. of tincture of digitalis per rectum there was a striking but temporary improvement. For the next three weeks there was a marked edema of the scrotum and penis, with edema of the lower extremities and fluid in the abdominal cavity. Tincture of digitalis, urea and salyrgan were of no avail in the treatment of this fluid accumulation. Salyrgan was administered as follows: On October 16, 1 cc. was given, October 19, 0.5 cc., October 22, 0.5 cc., October 29, 0.5 cc., November 3, 0.5 cc., and November 5, 1 cc. The patient expired on November 7, of cardiac insufficiency.

*Laboratory Data*—Urinalysis showed a specific gravity of from 1.019 to 1.026 and negative results for albumin and casts. The total daily volume of urine without salyrgan ranged from 125 to 400 cc., with salyrgan as much as 860 cc. was collected. The collection of urine was not possible after the development of edema of the penis and scrotum.

Examination of the blood made on July 25 showed 16 mg. of urea nitrogen per hundred cubic centimeters, a negative Wassermann reaction and 80 per cent of hemoglobin.

Roentgen examination of the chest showed moderate pulmonary congestion, a globular heart with a rounded and prominent left ventricle and pulmonary conus. On fluoroscopic examination the left auricle was seen to bulge into the retro-cardiac space. An electrocardiogram showed deviation of the left axis.

*Autopsy*—Autopsy was performed seven hours after death. The incision was limited to the chest. The body was that of a well nourished boy, 103 cm long. There was marked edema of the feet and genitalia. The glans penis felt almost cystic.

The anatomic diagnosis was chronic rheumatic heart disease, mitral stenosis and insufficiency, aortic insufficiency, cardiac hypertrophy and dilatation, chronic passive congestion of the viscera and mercurial nephritis (?). Only the positive observations are recorded.

The lungs were normal, except for numerous subpleural, petechial hemorrhages. The heart showed dilatation and hypertrophy, especially of the right ventricle. The mitral valve was slightly thickened at the edges. The aortic cusp had a few vegetations along the line of closure. The chordae tendineae were shortened and thickened. The posterior cusp of the aortic valve was also slightly thickened. The spleen was the seat of chronic passive congestion. The liver was large and soft and weighed 600 Gm. On section the lobules were well marked. The entire parenchyma was remarkably fatty and light.

The kidneys weighed 80 Gm each and measured  $8\frac{1}{2}$  by 4 by 3 cm. Both were somewhat flabby. On section the parenchyma was pale olive brown. The cortex was demarcated from the medulla by its bloodless appearance and lighter color. The pyramids were well defined. Some of them were slightly injected. Cortical rays, though perceptible with difficulty, were regular in arrangement. The pelvic mucosa was pale and smooth. The ureters showed no abnormalities.

The esophagus, stomach, colon and appendix showed no abnormalities. There were a few small petechial hemorrhages at the jejuno-ileal junction.

Microscopically, the salient observations aside from those in the kidneys were areas of fibrosis in the cardiac muscle and fatty degeneration in the liver with increase in the periportal fibrous tissue.

The kidneys showed a striking anemia of the glomeruli, though the rest of the organ exhibited evidence of chronic passive congestion. The capillary tufts were fairly large. There was no evidence of proliferation of the epithelial elements. The tubules showed an irregular distribution, with from a moderate to a severe degree of cloudy swelling. Many were filled with granular debris, and occasionally contained clumps of red blood cells. In some of the convoluted tubules small foci of calcification were present within the tubular epithelium, small calcific masses were occasionally found in the lumina of the tubules as well.

There was marked congestion of the capillaries of the interstitial tissue in contrast to the ischemia of the glomeruli. The blood vessels showed no abnormalities. The contrast of ischemic glomeruli in an organ otherwise the seat of passive congestion was consistent with a severe interference in glomerular function.

While experimentally in animals the criteria and diagnosis of mild hydraemia may readily be established, they are less clearly defined in human beings suffering from antecedent disease of the kidney. Harmon<sup>10</sup> has shown that the lesions of mercuric chloride poisoning

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<sup>10</sup> Harmon, E. L. Human Mercuric Chloride Poisoning by Intravenous Injection, *Am J Path* 4 321, 1928.

in man are the same whether the drug is administered by the parenteral or the oral route. The salyrgan was administered both intramuscularly and intravenously. Difficulties are to be expected when one seeks the finer anatomic criteria of hydrauryism in the kidneys of patients who have suffered from a long, debilitating illness, with chronic passive congestion of the viscera, or from a terminal acute infection. In the groups of older patients the presence of arteriosclerotic and arteriolosclerotic lesions with varying grades of destruction of the renal parenchyma made it difficult to determine the presence of changes specifically associated with mild mercurialism.

With these considerations in view, it was felt that only in the presence of a severe necrosis of the tubular epithelium or the characteristic calcium deposits, or both, was a diagnosis of mercurial poisoning justifiable on anatomic grounds.

As the accompanying table shows, these signs of hydrauryism in the kidneys studied were absent, with one possible exception. Such changes as were found are to be explained by the concomitant arteriosclerosis and arteriolosclerosis, by the terminal acute infection or by the chronic passive congestion. While it is true that cloudy swelling of the tubular epithelium occasionally presents itself in the absence of a diagnosis of pneumonia or other acute infection, it must be borne in mind that chronic passive congestion itself is sufficient to produce such a change.

The case reported, case 3, looks suspicious, in view of the remarkable anemia of the cortices of the kidney in an otherwise deeply congested cadaver. Furthermore, there were slight but definite deposits of calcium in the tubular epithelium and lumina. The tubular epithelium itself exhibited more than the usual amount of cloudy swelling, which amounted at times to a granular debris that filled the lumina, in the absence of an acute terminal infection. The clinical history warranted the use of strenuous measures in this case. The fact that the patient was a 5 year old child is not significant, since we have administered the drug repeatedly to children with severe congestive heart failure and no complications have ensued.

It is most remarkable that, despite the severe degenerative lesions present in many of the hearts and kidneys of our autopsy material the patients were not injured by the repeated injection of salyrgan. In one patient the amount injected was 130 cc. In a few instances the colonic mucosa was congested and edematous. Severe lesions were not observed.

Conclusions as to the toxicity of the mercurial diuretics based on animal experimentation must be applied with caution to man. John-

stone and Keith<sup>11</sup> found 0.05 cc of novasurol per kilogram toxic for rabbits if given repeatedly. Death was the result of a variable grade of nephritis. The impression that salyrgan in similar doses is less dangerous is not borne out by Moller<sup>12</sup>. He found that 0.04 cc per kilogram of the drug did not produce diuresis in rabbits, but resulted in albuminuria, while when 0.06 cc was given there were diuresis, albuminuria, red blood cells and casts in the urine. Pathologically, he found that renal damage could be demonstrated as early as four and a half hours after the injection. Repeated injection with this same dose at ten-day intervals resulted in chronic nephritis. In dogs, however, Moller found no evidence of renal irritation with as much as 0.06 cc of salyrgan per kilogram. He distinguishes the response in the rabbit from that in the dog, and believes that man approximates the latter in his behavior to the drug.

Fourneau and Melville<sup>13</sup> studied the pharmacologic action of eighteen separate mercurial preparations having diuretic properties. Depending on their chemical structure, these preparations could be divided into several groups. While the effect of the injection of salyrgan was not specifically observed, it is sufficiently close in structure to neptal, one of the drugs investigated, to allow one to apply the same conclusions. They found that the intake of fluid is an important factor in the determination of the toxic dose of mercurial diuretics in the rabbit and probably in other animals. The same doses were no longer fatal when 200 cc of distilled water was administered by stomach tube either shortly before or after the injection of the drug tested. According to them, the minimum toxic dose is that weight of the drug which when injected intravenously into an animal kept on a basal, water-free diet, leads to progressive emaciation and death of the animal in from seven to fourteen days after the injection. They found a toxicity for the separate groups which is fairly uniform for the individual members. It seems to be part of the chemical structure.

The different standard of toxicity employed by Fourneau and Melville yielded absolute values for the toxic doses of novasurol and salyrgan about three times those of previous investigators. Yet they too found the novasurol group less toxic than the salyrgan for the rabbit. These results are contrary to the general impression received by the clinical investigators cited previously and serve to illustrate the difficulty of transferring dosages from one species to another.

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11 Johnstone, B. I., and Keith, N. M. Toxicity of Novasurol, *Arch. Int. Med.* **42**, 189 (Aug.) 1928.

12 Moller, K. O. Untersuchung ueber die Pharmakologie des Salyrgans I, II, III, *Arch. f. exper. Path. u. Pharmacol.* **148**, 56, 67 and 81, 1930.

13 Fourneau, E., and Melville, K. I. Studies in Mercurial Chemotherapy I, II, J. *Pharmacol. & Exper. Therap.* **41**, 21, 1931.



# Comparative Toxicity of Salyrgan

No	Case No	Age	Period of Observation Mo	Salyrgan Dosage	Total Salyrgan Cc	Chief Anatomic Diagnosis at Autopsy	Comment on Kidney
1	18233	13	1	3 injections of 1 cc each two weeks before death	3	C R C V D, * acute rheumatic myocarditis C P C of viscera	Congestion of glomeruli and capillaries, rest of kidney appeared normal
2	15911	54	62	2 doses in last 5 days of life	4	Right heart failure secondary to long standing asthma and emphysema bronchiectasis C P C viscera	Diffuse arteriosclerosis with replacement fibrosis of moderate number of glomeruli, congestion throughout
3	16507	5	4	6 injections in last 3 weeks	4	C R C V D, see report of case	See report of case
4	16659	12	21	4 injections in last month of life	4	C R C V D fibrinopurulent pericarditis multiple old infarcts in the lungs, C P C of viscera	Marked congestion of medulla and cortex, with cloudy swelling of tubular epithellum
5	17041	53	1	3 injections in last 3 weeks of life	3	Syphilitic aortitis with destruction of aortic cusps, aortic	Arteriosclerosis and arteriolosclerosis with marked congestion of parenchyma
6	17167	54	10	3 injections in last 2 weeks of life	6	Chronic pulmonary emphysema, cardiac hypertrophy and dilatation, C P C of viscera bronchopneumonia	Areas of anemic infarction in left kidney moderate arteriolosclerosis
7	17947	11	8	4 injections of 1 cc each 3 months before death, 2 cc in last 2 weeks	6	C R C V D bronchopneumonia C P C of viscera	Moderate congestion granular degeneration of tubular epithellum
8	16855	61	2	1 injections in last 2 weeks of life	7	C R C V D, bronchopneumonia, C P C of viscera	Arteriosclerosis with replacement fibrosis of many glomeruli congestion, granular degeneration of tubular epithellum
9	14329R	65	53	4 injections in last month of life	8	C R C V D, C P C of all viscera	Diffuse arteriosclerosis with replacement fibrosis of many glomeruli
10	17919	54	2	4 injections including one on day of death	8	Coronary occlusion with myocardial infarction serofibrinous pleurisy	Arteriosclerosis moderate congestion, granular degeneration of tubules
11	15361R	39	5	6 injections 4 in last month of life	12	C R C V D C P C of viscera	Thrombosis of right renal vein old and fresh infarcts throughout kidneys widespread destruction of renal parenchyma
12	16533	34	3	Numerous injections before admission, 6 during stay	12+	C R C V D, C P C of viscera, adherent pericardium	Extreme congestion, granular degeneration of tubules
13	17368	68	3	6 injections in last 3 weeks of life	12	Coronary occlusion, myocardial fibrosis acute pericarditis, C P C of viscera	Arteriosclerosis and arteriolosclerosis, marked fragmentation and vacuolization of tubular epithellum
14	19464	64	10	6 injections in last 7 weeks of life, 1 on day before exitus	12	Hypertensive heart disease, coronary occlusion, C P C of viscera	Diffuse arteriosclerosis replacement fibrosis, congestion

15	14555R	60	25	Occasional dose at start of injections in last 2 months	11	Sclerosis of coronary arteries, myocardial fibrosis, anasarca	Diffuse arteriosclerosis with replacement fibrosis	
16	14945	26	12	7 injections in last 3 months of life	11	CRCVD, CPC of viscera	New and old infarcts in both kidneys, granular and fatty degeneration of tubules	
17	16900	59	9	4 injections at start, 3 in the last month of life	14	Syphilitic aortitis, generalized arteriosclerosis CPC of viscera	Arteriosclerosis moderate congestion, old and recent areas of infarction	
18	19197	63	29	Numerous injections before admission 8 in last 8 weeks of life	16+	Coronary artery disease CPC of viscera	Arteriosclerosis replacement fibrosis congestion	
19	14635R	62	10	10 injections in last 5 months of life	20	Cardiac hypertrophy and dilatation, CPC of viscera bronchopneumonia	Arteriosclerosis congestion granular degeneration of tubular epithelium	
20	19294	56	6	Several injections before admission, 10 during stay	20+	Coronary sclerosis and occlusion myocardial infarction, CPC of viscera	Marked congestion, diffuse arteriosclerosis with replacement fibrosis	
21	16283	57	12	14 injections throughout stay	28	CRCVD thrombosis of right pulmonary artery, CPC of viscera	Diffuse arteriosclerosis with replacement fibrosis, moderate congestion	
22	12554	30	22	18 injections in last 6 months of life	31	CRCVD, pulmonary infarction, CPC of viscera	Marked congestion, healed infarcts, granular degeneration of tubules	
23	16372R	63	12	18 injections in last 5 months of life	35	CRCVD, carcinoma of the lung, CPC of viscera	Diffuse arteriosclerosis with replacement fibrosis	
24	19192	49	34	30 injections during stay, wrist-drop developed after intramuscular injection	60	Cardiac hypertrophy and dilatation CPC of viscera	Diffuse arteriosclerosis, congestion, granular degeneration of tubules	
25	17095	46	7	37 injections during hospital stay	74	Cardiac hypertrophy and dilatation, CPC of viscera, bronchopneumonia	Arteriosclerosis and arteriosclerosis with replacement fibrosis, congestion	
26	16270R	60	20	38 injections during hospital stay	76	CRCVD, coronary occlusion, CPC of all viscera	Diffuse arteriosclerosis with replacement fibrosis, marked congestion	
27	18291	24	30	Numerous injections before admission, 43 during stay	86+	CRCVD, CPC of viscera	Intense congestion so marked that glomeruli appear swollen	
28	19220	39	12	Frequent injections before admission 48 during hospital stay	96+	Cardiac hypertrophy and dilatation, CPC of viscera	Diffuse arteriosclerosis, replacement fibrosis, granular degeneration of tubular epithelium	
29	14301R	36	22	Numerous injections before admission, 54 during hospital stay	108+	CRCVD CPC of viscera, bronchopneumonia	Diffuse arteriosclerosis with replacement fibrosis	
30	19773	54	12	65 injections during hospital stay many others before admission	130+	Coronary artery disease with old and recent occlusions CPC of all viscera	Diffuse arteriosclerosis with replacement fibrosis marked congestion	

\* CRCVD means chronic rheumatic cardiovascular disease and CPC chronic passive congestion

Salyrgan is dispensed in a 10 per cent aqueous solution, each cubic centimeter of which contains about 40 mg of mercury<sup>14</sup> Though it is apparently harmless on the basis of the mercurial content, it must be borne in mind that nearly 80 per cent of the mercury is excreted in the urine within twenty-four hours<sup>12</sup> While the usual dose is 2 cc every two to three days, single doses of 4 and 5 cc have been injected without ill effect<sup>9</sup> When the diuretic response is absent after the injection of 2 cc of salyrgan, it would be a much safer and more effective procedure to resort to the adjuvant therapy of the acid-producing salts rather than to larger doses of salyrgan Important as well is the fluid content of the body The edema may act as a protective device against the mercurial intoxication, even as excess amounts of water spare the rabbit<sup>13</sup> and the dog<sup>15</sup> suffering from mercury poisoning

#### SUMMARY

1 The comparative toxicity of salyrgan and novasurol is reviewed from the clinical and experimental results reported in the literature

2 The inconsistency between the clinical findings and the results of animal experimentation is noted

3 In more than 3,000 injections of salyrgan given at the Montefiore Hospital only two instances of mild stomatitis were encountered when the drug was administered to patients with impaired renal function In one patient wrist-drop developed and in two foot-drop following faulty intramuscular injection

4 Anatomic studies were made of thirty patients with congestive heart failure who were given repeated injections with doses of salyrgan up to 130 cc

5 In one case a lesion suggestive of mercurialism was found at autopsy in the kidney

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14 Collins, G W Chemical Examination of Salyrgan J A M A **91** 1994 (Dec 22) 1928

15 Haskell, C C, Carder, J R and Coffindaffer R S The Value of Forcing Fluids in the Treatment of Mercuric Chloride Poisoning, J A M A **81** 448 (Aug 11) 1923

# Book Reviews

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**History of Medicine in the United States** By Francis R Packard  
Price, \$12 Pp 1323 New York Paul B Hoeber, Inc, 1931

This book is a successor to Packard's well known "History of Medicine in the United States," which has long been out of print. The first volume is in the form, for the most part, of a narrative history of medicine in the United States, but the second volume contains a series of articles on the history of various aspects of medicine to present times. The book is to be judged, therefore, rather as a treasure of information on the history of American medicine than as a consecutive account. Its scope is best shown by its table of contents.

## Volume I

- I Medical Events Connected with the Early History of the English Colonies in America
- II Epidemic Sickness and Mortality in the English Colonies in North America from Its Earliest Discovery to the Year 1800
- III Early Medical Legislation
- IV The Earliest Hospitals
- V Medical Education Before the Foundation of Medical Schools
- VI The Earliest Medical Schools
- VII Pre-Revolutionary Medical Publications
- VIII The Medical Profession in the War for Independence
- IX The Medical Department of the Army from the Close of the Revolution to the Close of the Spanish-American War

## Volume II

- X History of the Medical Department of the United States Navy
- XI Some of the Medical Schools Founded During the First Half of the Nineteenth Century
- XII Outlines of the Development of Medical Practice and Education in Some of the States
- XIII Foreign Influences on American Medicine
- XIV Some Notable Events in American Medicine and Surgery

## Appendices

- A* The Examination of Dr Church
- B* Clinical Lecture Delivered by Dr Thomas Bond Before the Managers of the Pennsylvania Hospital on Nov 26, 1766
- C* Surgeon Generals of the United States Army from the Organization of the Medical Department in 1818 to 1931
- D* The Humane Society of Philadelphia
- E* The Ether Controversy
- F* Items of Information on the Organization of Medical Education Compiled from Various Sources
- G* American Journal of the Medical Sciences
- H* The Boston Medical and Surgical Journal
- I* Some Homeopathic Medical Colleges
- J* Women in Medicine
- K* The Botanic, Physio-Medical and Eclectic Schools of Medicine in the United States

The volumes contain a vast collection of information, and a laborious and useful work has been done in their preparation. Few facts in the history of

American medicine to recent days have been omitted. In the second volume there is a good deal of inequality, and there are some inaccuracies, owing to the material with which the author has had to deal. The history of American medicine has been recorded much less carefully and completely in some parts of the country than in others. But, as the author says, "If I were to have waited to acquire the material for a complete history of medicine in the United States down to any selected date, let us say even as early as 1850, I would never have been able to fulfil my purpose, which is to present to those interested as much material bearing on the history of medicine in America as I could collect, in the fond hope that some more capable hands may be found to fill out the gaps."

Dr Packard has done well an important service. He has recorded in permanent form a great quantity of historical facts to make the future historian's task easy. He has also produced a work that the present-day reader will find interesting and useful, no matter in which phase of medical history he is interested.

**Der Herzalternans.** By Dr Med Bruno Kisch, Ord Professor der Physiologie an der Universität Köln. Price, 12 marks. Pp 214, with 54 illustrations. Dresden. Theodore Steinkopff, 1932.

This monograph is, in deed and in truth, an exhaustive presentation of what is known (and of most that is thought) about the subject of alternation of the heart. Written by a physiologist who has contributed extensively to the experimental investigation of alternation, the theoretical and experimental aspects are surveyed with comprehension and are presented briefly and accurately. No phase of the relationship of alternation to the various types of cardiac disease or to abnormalities of rate or rhythm is omitted. The literature has been scrutinized from the time of Traube, who, in 1872, first differentiated the *pulsus alternans* from the *pulsus bigeminus*. The historical matter presented is an interesting commentary on the acumen of the clinicians of the latter half of the nineteenth century, and the ingenuity and scientific spirit of the men who have developed the methods of modern physiology. Approximately one third of the book is devoted to the results of the study of alternation by the usual procedures of physical examination and the aid of various modern mechanical methods. Consideration of the mechanics and the nature of alternation is followed by the author's explanation of his coefficient of cardiac alternation. Fundamentally, alternation is an expression of bio-energetic states of the cardiac muscle which may result under various influences. The clinical section is brief, but the application of the earlier discussions to the clinical problems is convincing and illuminating. Indeed, the entire monograph is so interesting and valuable to the clinician that, to the reviewer, a separate section on the clinical aspects of the subject came as somewhat of a surprise. The clinical section embraces a review of the literature by a master of the experimental and purely scientific aspects of the subject. This little book is a valuable addition to the literature of cardiovascular disease, it is scholarly and succinct, yet complete, characterized by its unity of thought and clarity of expression. An extensive bibliography adds to the value of the book.

**Quantitative Clinical Chemistry. Volume I. Interpretations.** By John P. Peters, M.D., M.A., Professor of Internal Medicine, Yale University, and Donald D. Van Slyke, Ph.D., Sc.D., Member of the Rockefeller Institute for Medical Research. Cloth. Price, \$12. Pp 1,269, with many tables and figures. Baltimore. Williams & Wilkins Company, 1931.

This volume represents the results of an exhaustive study and compilation of the numerous studies on chemical composition of the blood and urine and the interpretation of the values from the general biochemical, physiologic and clinical points of view. It is an excellent treatment of an involved subject that is in a continuous state of flux. In fact, some of the methods on which certain values of

the chemical composition of the blood are based are so nonspecific and frequently so inaccurate that when interpretations are made these limitations should be emphasized. Unfortunately such methods are changed so frequently by various workers that even an empiric comparison of the results from various laboratories cannot be made without some reservations or assumptions. The book obviously is written so that it should be of interest and value to the alert clinician as well as to his academic colleague. In each of the twenty-one chapters the more fundamental biochemistry of the particular subject under discussion is reviewed briefly without being too elementary, then follow in order comments on metabolism, the chemical composition of the blood and urine, and the clinical considerations in pathologic conditions. An extensive bibliography is added at the close of each chapter. The best chapters are devoted to (1) hemoglobin and oxygen, (2) carbonic acid and acid-base balance, (3) chlorides, (4) total organic acids and total base. Why the curious statement that cholesterol contains choline was made is a mystery. An extensive and excellent index makes the work extremely valuable.

**Prohibiting Minds and the Present Social and Economic Crises** By Stewart Paton, M.D., Lecturer on Psychiatry, Johns Hopkins University, Baltimore. Price, \$2. Pp 198. New York: Paul B. Hoeber, Inc., 1932.

Although dedicated to the "Therapeutic Club," this is not a medical book but a philosophical essay by an author eminent in biology and psychiatry. It touches on the field of mental hygiene, in which Paton was one of the pioneers, and it is undoubtedly his passion for sane thinking that has driven him to write this book. He deplores present-day squandering of nervous energy and the fast pace that does not give people time to balance their emotional and mental budgets. The people who advocate prohibitions of all kinds are characterized as "neurotics, as feelers not thinkers, who are as unprepared as children to direct the course of events in the political, economic or social world. Whatever does not meet with their approval they try to prohibit. Driven by fear of the past and bewildered by the present state of affairs they are swept off their feet by waves of prohibiting mania." "The mental reactions of the leaders of Prohibition in America and Communism in Russia constantly remind us of the emotional attitudes of disobedient children, haunted by Father images and obsessed by fear of parental discipline. Lacking in real independence they think that the control of human activities is merely a matter of authority, in which visions of governmental, ecclesiastical or legal representatives take the place of Father images. The fear that the Prohibitionists have of alcohol has been as effective as the Communists' fear of capitalism in preventing a great many people from becoming temperate, sane and peaceful." These quotations from the preface indicate the scope of the book, which is divided into three chapters: (1) Civilization—Shock, (2) Remedies, (3) Educating the Intellectuals.

**Problème sous-hepatiques** By Gaston Parturier. Price, 32 francs. Pp 272. Paris: Gaston Doin, 1931.

The author considers three problems in the subhepatic region: anatomy, pain and tumors. He spends considerable time emphasizing the fact that the relationship of the gallbladder to adjacent structures in the living subject is different from that observed in the cadaver. The relationships also change with different positions of the body and with pathologic processes. He advises the use of the Trendelenburg position for examination.

Acute and chronic painful conditions in the subhepatic region are discussed, and differential diagnosis is considered. Three types of pain in the gallbladder are described. One is mechanical, owing to the passage of gallstones, another is caused by infection, and the third, "colloidoclosique," is due to an unstable vegetative nervous system and endocrine factors. Treatment is given as follows: for the mechanical type, injections of morphine; for the infectious type, opium, antipyrine

for the fever (given by enema if necessary) and local applications of heat, and for the third type, local applications, with the injection of cocaine. Opiates are contraindicated in the last form.

The importance of laboratory work, especially duodenal drainage and radiology, is emphasized in connection with chronic conditions and tumors. It is advised that patients with the latter conditions, with certain exceptions, be treated first by rest, diet and proper medication. If these are not successful, if jaundice persists or if a tumor grows, surgical intervention is indicated.

This book may be summarized as a fair clinical review of conditions in the upper part of the abdomen.

**Nutrition** Volume 1 No 4 Direction of P. Carnot, M. Loeper and M. Villaret Price, 150 francs per year Pp 367 to 466 Paris Gaston Doin, 1931

This is a periodical published six times a year, containing papers on clinical, biologic and therapeutic subjects. Volume 1, no 4, 1931, is devoted to the gallbladder. It contains articles entitled as follows: "The Influence of Certain Pharmacodynamic Agents on the Contractility of the Gallbladder," "Biliary Disinfection," "Medication for Relaxing the Gallbladder," "Medical Treatment of Chronic Cholecystitis Without Stone," "Hepato-Biliary Action of Vichy Water Collected at the Spring and Tested by Duodenal Tubage, and "Hydromineral Treatment of Hepatic Insufficiency."

In discussing biliary disinfection, the statement is made that sodium bicarbonate changes the  $p_H$  of the bile and creates a sterility of the biliary passages, and that hence it is of therapeutic value in cases of chronic hepatitis and cholecystitis. The evidence offered is quite inadequate. The author of the section states that Vichy water is a definite chologogue. This conclusion is based on detailed analyses of bile obtained by duodenal drainage, but again the data given are insufficient. Hydromineral therapy is recommended for the treatment of chronic disease of the liver and gallbladder, but satisfactory evidence is not presented.

Several abstracts of the current literature on the gallbladder are included in the publication.

**Krankheitsanfaenge bei chronischen Leiden** Herausgegeben von Prof. Dr. A. Fraenkel Price, 4 marks Pp 174 Leipzig Georg Thieme, 1931

This monograph contains seventeen articles, each by a different author, and all concerned with the earliest manifestations of a group of chronic diseases.

Fraenkel's article opens with a general discussion of the subject. There follow a chapter on health examinations, life insurance examinations and then a brief discussion of the earlier manifestations of chronic nephritis, thyrotoxicosis, diabetes mellitus, cardiac decompensation, digitalis in early heart failure, the dynamics of cardiac failure, predominating manifestations of schizophrenia, psychosis, the beginning of alcoholism, early manifestation of tabes and paresis, early pulmonary tuberculosis, hepatic insufficiency and fundamental liver diagnosis.

The various subjects have been gone into thoroughly, and the reader may find in this monograph a good critical review of the present knowledge. This volume supplies an actual need, and furnishes a much needed ready reference on this field. Apparently all the contributors are well informed on their special topics and carried on more or less intensive research.

## PERICARDITIS

### I CHRONIC ADHERENT PERICARDITIS

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Adherent pericarditis is acknowledged to be one of the most difficult cardiac conditions to diagnose, and this statement is confirmed by analysis of records of necropsies. In relatively few cases is the condition positively identified while the patient is alive.

Numerous reasons exist for this inaccuracy of diagnosis. Foremost among them is the clinician's lack of suspicion regarding the possible existence of the disease. There may be complete absence of symptoms and signs, and this obviously renders identification of the disease impossible. The didactic overemphasis on so-called characteristic signs has gone far toward frustrating correct diagnosis, for in reality such signs exist in relatively few cases, and their absence often influences the clinician against committing himself. The occurrence of associated disease entirely unrelated to the cardiovascular system may so dominate the clinical picture that attention may be exclusively centered on the principal disease. Likewise, associated disease of the heart may apparently satisfactorily explain the patient's symptoms, and thought of additional pathologic change in the heart is summarily dismissed.

This investigation was undertaken with the foregoing facts clearly in mind, to determine, if possible, additional data and correlation that might be instrumental in more accurate diagnosis of a hitherto elusive disease.

### MATERIAL

The records of necropsies of the Mayo Clinic were critically studied, and among the 8,912 cases, 373 cases of pericarditis were found, an incidence of 4.2 per cent. The incidence in this group is considerably smaller than in those previously studied and reported on. Wells,<sup>1</sup> in 1,048 cases examined post mortem, found pericarditis in 11.3 per cent, Locke,<sup>2</sup> in 3,683, demonstrated pericarditis in 16.6 per cent, Musser

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From the Section on Cardiology, the Mayo Clinic.

1 Wells, H. G. The Pathology of the Healed Fibrous Adhesions of the Pericardium, *Am J M Sc* **123** 241 (Feb.) 1902.

2 Locke, E. A. The Occurrence and Diagnosis of Pericarditis, *Boston M & S J* **175** 590 (Oct 26) 1916.



and Herrmann,<sup>3</sup> in 1,720, found pericarditis in 17.7 per cent. In the 15,363 cases examined post mortem, just mentioned, pericarditis was found to occur in 1,406, an incidence of 9.2 per cent.

In the series from the Mayo Clinic, adherent pericarditis occurred in 144 (that is, in 38.4 per cent of the cases of pericarditis). These 144 cases form the basis for this study.

*Sex and Age Incidence*—Males predominate in our series. There were one hundred males (69.4 per cent) and forty-four females (30.6 per cent). This observation is borne out by previous studies. Musser and Herrmann in their study of forty-six cases of adherent pericarditis recorded that these occurred in males only.

A greater number of patients were in the later than in the earlier periods of life, sixty-eight (47.2 per cent) were in the sixth and seventh decades. One hundred eight patients (75 per cent) were between the ages of 30 and 70 years, the most productive period of life. The youngest patient was 2 years of age, had extensive parietal adhesions, and died of heart failure. The oldest patient was 85 years of age. The average age for all was 48.8 years.

*Etiologic Conditions*—Definite etiologic diseases were determinable in seventy-three cases (50.7 per cent). Rheumatic fever occurred with greatest frequency, it was present in thirty-one cases (21.5 per cent). Rheumatic fever may have been an influence in other cases and not recognized, for previously identification of rheumatic fever rested chiefly on the presence of articular involvement, which is now known not to be a constant accompaniment.

Intrathoracic infection occurred next in frequency, twenty-five cases (17.4 per cent) were recorded.

Cardiac infarction occurred in nine cases (6.2 per cent). It is a condition that ordinarily is not accorded much consideration as a cause of adherent pericarditis. It is well known, of course, that cardiac infarction is frequently complicated by localized pericarditis overlying the region of myocardial destruction, a sterile inflammatory reaction. With healing of the infarct and recovery of the patient, the pericardial involvement resolves in the usual manner, with the result that a considerable portion of the pericardial sac becomes obliterated by fibrous adhesions.

Syphilis occurred as a possible etiologic disease in only four cases (2.8 per cent). In two of these cases, aortic aneurysm was present, in one, a dissecting aneurysm, with ultimate rupture into the pericardium, and in the other, a saccular aneurysm of the ascending portion. In both cases, the pericardial involvement could possibly have resulted from the

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3 Musser, J. H., and Herrmann, G. R. Chronic Pericarditis. The Clinical and Experimental Aspects, J. A. M. A. 87:459 (Aug. 14) 1926.

mechanical effects of the aneurysms, whereas in the remaining two cases it is possible that some other infectious process may have been causal, although syphilis was the outstanding disease in the production of cardiovascular injury. The pericardial cavity was only partially obliterated in all of these cases.

Neoplastic invasion of the pericardium, with resulting pericardial reaction and partial obliteration of the sac, occurred in four cases (2.8 per cent). The invasion occurred through metastasis in two instances: in one case from a sarcoma of the stomach, and in the other, from a sarcoma of the left ovary. In two cases, the pericardium became involved by direct extension of a contiguous malignant tumor. A primary carcinoma of the left lung invaded the pericardium in one case, and an intrathoracic lesion of Hodgkin's disease in the other.

The intrathoracic infections comprised the following conditions: chronic obliterative pleuritis with involvement of the pericardium in fourteen cases (5.6 per cent), in two of which tuberculosis was present; chronic empyema with pleural and pericardial involvement in six cases (2.4 per cent); chronic mediastinitis in three cases (1.2 per cent); miliary tuberculosis with extensive invasion of the pericardium in one case (.4 per cent), and purulent bronchitis with pulmonary abscesses in one case (.4 per cent).

There were seventy-one cases (49.3 per cent) of adherent pericarditis in which definite evidence of etiologic diseases was not found. It seems probable that in numerous instances apparently trivial infections take place that result in acute fibrinous pericarditis; these conditions are not recognized at the time of their occurrence, they undergo spontaneous abatement, and ultimately result in partial or complete obliteration of the pericardial sac.

#### PATHOLOGIC DATA

The cases were divided into three groups according to the character of the pericardial involvement.

The pericardial sac was completely obliterated in fifty-three cases (36.8 per cent). In seventy-nine cases (54.9 per cent) the sac was partially obliterated, but in all of these instances to a considerable degree. The remaining twelve cases (8.3 per cent) were characterized by the presence of fairly extensive parietal adhesions to the surrounding structures.

Well marked calcification of portions of the pericardium occurred in fifteen cases (10.4 per cent). This phenomenon is probably the end-result of inflammatory disease. Case <sup>4</sup> stated that in such cases almost

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<sup>4</sup> Case, J. T. Pericarditis Calculosa. Report of a New Case Discovered Roentgenologically, J. A. M. A. **80** 236 (Jan. 27) 1923.

without exception the visceral and parietal layers of the pericardium are united by a plastic process. In the present study, however, the pericardial sac was only partially obliterated in eight cases in which calcification was well marked, whereas the obliteration was complete in three. Calcification of the pericardium, evidenced in the life of the patient by means of roentgenography, has been reported by several authors, whose names will appear in the bibliography of a later article.

*Weight of the Heart*—The weights in 107 cases (74.3 per cent) were available for study. Two cases were excluded from our computations, owing to inclusion of a greatly thickened pericardium in one case and inclusion of a metastatic growth in another. In table 1 are given the cardiac weights in the 105 remaining cases, grouped according to 100 Gm. spreads. In 87.7 per cent of the cases, the weights of the heart were in excess of normal. According to the studies of Smith,<sup>5</sup>

TABLE 1—*Weight of the Heart in the One Hundred and Five Cases in Which It Was Known \**

Weight, Gm	Cases	Percentage
100-199	1	0.9
200-299	12	11.5
300-399	27	25.7
400-499	21	20.0
500-599	17	16.2
600-699	13	12.4
700-799	6	5.8
800-899	5	4.6
900-999	3	2.9

\* Average cardiac weight, 478.1 Gm.

the average normal weight of the heart of the adult male is 294 Gm., whereas the average normal weight of the heart of the adult female is 250 Gm. The average weight of the heart in the group of cases under investigation was 478.1 Gm. The minimal weight of the heart was 135 Gm., whereas the maximal weight was 950 Gm.

If the cases are analyzed according to the three major pathologic groups, (1) complete obliteration of the pericardial sac, (2) partial obliteration of the pericardial sac and (3) parietal adhesions, very interesting differences in average cardiac weights appear (table 2).

These data in general are in agreement with those of Musser and Heilmann, who obtained average weights, in the three groups, of 536.6 Gm., 443 Gm. and 384 Gm. It must be remembered that the presence of cardiac hypertrophy in many of the cases was not solely the result of adherent pericarditis, for associated cardiac lesions existed that were also responsible for the increase in mass of muscle.

<sup>5</sup> Smith, H. L. The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age, *Am. Heart J.* 4:79 (Oct.) 1928.

*Associated Cardiac Disease*—Associated disease of the heart occurred in seventy-seven cases (53.5 per cent). Lyter,<sup>6</sup> in a study of thirty cases of chronic pericardial adhesions, called attention to associated cardiac conditions.

The disease that occurred most frequently was coronary sclerosis, this was well marked in the thirty-one cases (21.5 per cent) recorded.

TABLE 2—*Weight of the Heart in All One Hundred and Five Cases in Which It Was Known, Classified on the Basis of Degree of Obliteration of Pericardial Sac*

Weight, Gm	Complete Obliteration, 42 Cases		Partial Obliteration, 57 Cases		Parietal Adhesions, 6 Cases	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
100-199			1	1.8		
200-299	6	14.3	4	7.0	2	33.3
300-399	11	26.2	13	22.8	3	50.0
400-499	8	19.0	11	19.3	1	16.7
500-599	6	14.3	12	21.0		
600-699	7	16.7	6	10.5		
700-799	1	2.4	5	8.8		
800-899	2	4.7	3	5.3		
900-999	1	2.4	2	3.5		
Average weight	472.7 Gm		506.5 Gm		251.2 Gm	

TABLE 3—*Data Concerning Seventy-Seven Cases of Adherent Pericarditis in Which There Was Associated Cardiac Disease, Together with Sixty-Seven Cases in Which There Was Chronic Adherent Pericarditis Only*

Pathologic Diagnosis	Cases	Per Cent*	Average Age, Yr	Average Cardiac Weight, Gm †
Coronary sclerosis	31	21.5	61.3	512.8
Rheumatic heart disease (mitral stenosis)	25	17.4	37.0	478.1
Hypertensive heart disease	11	7.6	53.4	554.1
Rheumatic heart disease (aortic insufficiency)	6	4.2	27.6	891.0
Aortic syphilis	4	2.8	56.5	550.0
No associated cardiac disease	67	46.5	47.8	413.4

\* The percentage is calculated on the basis of 144 (77 + 67). The total percentage of cases in which there was associated cardiac disease was 53.5.

† The average weight of the hearts in all cases in which there was associated cardiac disease, in which the weight of the hearts was known, was 536 Gm.

in table 3. The average degree of involvement was graded 3. Hypertension was present in eight of these thirty-one cases, healed cardiac infarction in five, recent cardiac infarction in four and the myofibrosis of gradual circulatory obliteration in four. This is not a complete record of all conditions associated with coronary sclerosis, for instance, some cases of rheumatic heart disease might be mentioned in this connection, but they are not, because the same cases are mentioned in the consideration of conditions associated with rheumatic heart disease.

6 Lyter, J. C. Incidence, Associated Pathology and Clinical Diagnosis of Chronic Pericardial Adhesions, *Am J M Sc* **159**: 891 (June) 1920.

The pericardium was completely obliterated in eleven of these thirty-one cases and partially obliterated in eighteen, parietal adhesions existed in two of them. The lowest cardiac weight was 230 Gm, and the greatest cardiac weight, 900 Gm. In order to determine the influence of hypertension on cardiac weight, the average weight of the hearts in the eight cases with hypertension was compared with the average weight of the hearts in the remaining twenty cases of coronary sclerosis. The average weight of the hearts in the cases with hypertension was 657.1 Gm, in the cases without hypertension, 497.1 Gm. It must be recalled that the presence of adherent pericarditis materially influenced the cardiac weights in these groups. Also, Smith and Bartels<sup>7</sup> and others clearly showed that the heart that has survived infarction for a considerable period may increase its muscle mass. In the cases of healed and chronic infarction taken together, the average cardiac weight was 557.3 Gm, a figure greater than the average for the entire group of cases of coronary sclerosis. The age incidence of the cases of coronary sclerosis was of wide range, the youngest patient was 31 years of age, and the oldest, 85 years.

Rheumatic heart disease with mitral stenosis occurred next in order of frequency. The associated lesions in this group comprised one case each of the following: coronary sclerosis, graded 2, aortic insufficiency, aortic and tricuspid insufficiency, and aortic stenosis and hypertension. The pericardial sac was completely obliterated in nine cases and partially obliterated in fifteen cases, parietal adhesions were present in one case. The average cardiac weight was as it is given in table 3. The minimal cardiac weight was 280 Gm, and the maximal weight, 800 Gm. The youngest patient in this group was 10 years of age, the oldest, 73.

Hypertensive heart disease occurred in eleven cases (7.6 per cent). Complete obliteration of the pericardial sac was present in two cases, and in nine cases the obliteration was partial. The smallest heart weighed 300 Gm, the largest, 930 Gm. The youngest patient was 22 years of age, and the oldest, 66.

Rheumatic heart disease with aortic insufficiency occurred in six cases (4.2 per cent). Five patients had associated mitral disease, although the aortic lesion dominated. In three cases there was complete obliteration, and in three, partial obliteration of the pericardial sac. The minimal cardiac weight was 832 Gm, and the maximal weight, 950 Gm. The weights of the hearts were greater in this group than in any other. The youngest patient was 6 years of age, and the oldest, 58.

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<sup>7</sup> Smith, H. L., and Bartels, E. C. Coronary Thrombosis with Myocardial Infarction and Hypertrophy in Young Persons. A Report of Two Cases with Necropsy, *J. A. M. A.* **98** 1072 (March 26) 1932.

Aortic syphilis occurred in only four cases (28 per cent). These cases comprised one of aortitis with aortic insufficiency, one of dissecting aneurysm of the thoracic aorta with rupture into the pericardial cavity, one of aortitis and one of aortitis with aortic insufficiency and a sacular aneurysm of the ascending aorta. The pericardial sac was only partially obliterated in all cases. The lowest cardiac weight was 500 Gm, and the greatest, 600 Gm. The youngest patient was 38 years of age, and the oldest, 81.

Adherent pericarditis as the only cardiac disease occurred in sixty-seven cases (46.5 per cent). The pericardial cavity was completely obliterated in thirty cases (44.8 per cent). The obliteration was only partial in thirty-one cases (46.3 per cent), and parietal adhesions existed in six cases (8.9 per cent). The relationship of average cardiac

TABLE 4—*Weight of the Heart in the Forty-Four Cases in Which It Was Known, of the Sixty-Seven Cases in Which Adherent Pericarditis Was the Only Cardiac Disease Present, Classified on the Basis of Degree of Obliteration of the Pericardial Sac*

Weight, Gm	Complete Obliteration, 19 Cases		Partial Obliteration, 22 Cases		Parietal Adhesions, 3 Cases	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
100-199			1	4.5		
200-299	3	15.8	3	13.7	2	66.7
300-399	8	42.2	7	31.8	1	33.3
400-499	3	15.8	6	27.3		
500-599	3	15.8	2	9.1		
600-699	1	5.2	1	4.5		
700-799			2	9.1		
800-899	1	5.2				

weights in these major pathologic groups (based on degree of obliteration of pericardial sac) differs from that in the earlier portion of this paper, when the cases were analyzed regardless of associated cardiac disease. On recalling those figures (table 2), it is found that the greatest average cardiac weight occurred in the cases with partial obliteration of the pericardial sac (506.5 Gm). In cases in which the sac was completely obliterated, the average weight of the hearts was less (472.7 Gm), and in cases in which parietal adhesions existed, the smallest average cardiac weight was found (251.2 Gm). However, when uncomplicated cases of adherent pericarditis are considered, cases in which other cardiac diseases capable of producing cardiac hypertrophy were not present, this relationship no longer obtains. There was practically no difference between the average weights of the hearts in cases in which the pericardial sac was partially obliterated, and in cases in which it was completely obliterated (table 4). In cases accompanied by parietal adhesions, however, the average weight of the hearts was lower. The latter group comprised only three cases, which permits a large ele-

ment of error, but the average weight is in general agreement with the larger series of cases. These figures indicate that the mechanical effect on cardiac hypertrophy of partial obliteration of the pericardial sac does not materially differ from that of complete obliteration. However, a considerable difference in effect is evident so far as parietal adhesions are concerned. It seems proper to conclude that complete and partial obliterations of the sac interfere with the action of the heart to a far greater degree than do parietal adhesions. The youngest patient of those with uncomplicated adherent pericarditis was 2 years of age, and the oldest, 73. The average age was 47.8 years, as has been seen in table 3. This closely approximates the average age of patients with associated cardiac disease, which was 47.1 years. In the cases in which adherent pericarditis was the only cardiac disease, and in which there was partial obliteration of the pericardial cavity, the fluid content was either increased in amount or altered in character in eighteen (22.7 per cent) of the cases in which the amount of fluid present was recorded. Clear fluid was found to be present in quantities varying from 40 to 1,000 cc. in six cases, pus was present in four cases, varying in amount from 5 to 300 cc., and the fluid was turbid or bloody in the remaining eight cases.

#### CLINICAL FEATURES

It is significant that in a group of 144 cases of adherent pericarditis in which necropsy revealed well marked involvement, only fifty-seven patients (39.5 per cent) presented complaints that made the heart the major issue in the clinical picture. This relatively small incidence is additional testimony to the fact that comparatively asymptomatic adherent pericarditis frequently exists, and is additional explanation of why many cases are overlooked in the course of the lives of the patients. Those patients who presented outstanding cardiac symptoms were to a large extent those who had associated cardiac disease. Of the fifty-seven patients, forty-seven (82.4 per cent) had associated cardiac disease, whereas only ten (17.6 per cent) had adherent pericarditis without any other pathologic condition of the heart. Only three cases of polyserositis were found in the entire group of fifty-seven. Among these cases in which cardiac symptoms and findings predominated, rheumatic heart disease with mitral stenosis occurred in nineteen cases. Other diseases in order of frequency were coronary sclerosis, sixteen cases, adherent pericarditis only, ten cases, rheumatic heart disease with aortic insufficiency, six cases, aortic syphilis, four cases, and hypertensive heart disease, two cases.

The eighty-seven cases in which adherent pericarditis was but an incidental, practically asymptomatic condition comprised a very miscellaneous group. Carcinoma was the outstanding disease in twenty-seven

of these cases (31 per cent), nephritis, in eight, sarcoma, in six, cholecystitis and septicemia, each in four, benign prostatic hypertrophy, pulmonary abscess, empyema and tuberculosis, each in three, tumor of the brain, adenomatous goiter with hyperthyroidism, ulcerative colitis, hepatic cirrhosis, chronic arthritis, ventral hernia and intestinal obstruction, each in two, perforated peptic ulcer, purpura hemorrhagica, calculi of the urinary bladder, psychosis, salpingitis, pernicious anemia, Hodgkin's disease, trifacial neuralgia, diabetes mellitus, bronchiectasis, cerebral hemorrhage and pneumonia, each in one

There were no physical signs that occurred with sufficient uniformity to permit of their being considered characteristic of adherent pericarditis. Murmurs frequently occurred, but their time, quality, situation and transmission were not unusual, and they were largely present in cases with associated valvular disease. Pericardial friction rubs were audible in only eight cases.

Briefly reviewed, some of the signs that have been said to be characteristic of adherent pericarditis are as follows:

1. Kussmaul's<sup>8</sup> sign. The veins of the neck may fill during inspiration, accompanied by inspiratory diminution in the size of the pulse, and at times by absence of some beats during inspiration (pulsus paradoxus). This phenomenon is very occasionally observed.

2. Friedreich's<sup>9</sup> sign. By this is meant collapse of the veins of the neck, diastolic in time. This is not uncommon in heart failure resulting from various causes.

3. Broadbent's<sup>10</sup> sign. This consists in visible retraction of the back in the region of the eleventh and twelfth ribs, synchronous with cardiac systole. This sign, when present, is characteristic of parietal adhesions.

4. Cooper's<sup>11</sup> sign. This sign is elicited by determination of the length of time it is possible for the patient to hold the breath in inspiration, and, five minutes later, the same for holding the breath in expiration. Normal persons, it is said, can hold the breath in inspiration for from forty to seventy seconds, and in expiration for from twenty to twenty-five seconds. In case of heart disease, the values are said to be inspiration twenty-five seconds, and expiration fifteen seconds. In

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8 Kussmaul, A. Ueber schwierige Mediastino-Pericarditis und paradoxen Puls, *Berl klin Wchnschr* **10** 433 (Sept 15) 1873.

9 Friedreich, N. Ueber den Venenpuls, *Deutsches Arch f klin Med* **1** 241 (Nov) 1865.

10 Broadbent, W. H., and Broadbent, J. F. H. *Heart Disease, with Special Reference to Prognosis and Treatment*, ed 3, New York, William Wood & Company, 1900, p 249.

11 Cooper, C. M. The Respiratory Ratio. A Preliminary Note, *J. A. M. A.* **52** 1182 (April 10) 1909.



cases of mediastinal and pericardial adhesions, a paradoxical ratio is said to occur, namely, inspiration nine seconds, and expiration twenty-five seconds

*Roentgenography*—The heart was examined roentgenologically in fifty-four cases (37.5 per cent). Varying degrees of cardiac enlargement were found in thirty-four cases (62.9 per cent). There did not appear to be any characteristic contour, this, in part at least, was because the majority of patients subjected to this method of examination had associated cardiac disease, and the contour of the heart would naturally show the effect of the given lesion on the myocardium.

*Electrocardiography*—When extensive fixation of the heart occurs, particularly by mediastinopericarditis and parietal adhesions, probably the most constant electrocardiographic feature is fixation of the electrical axis as shown by Dieuaide.<sup>12</sup>

TABLE 5—*Electrocardiographic Findings in Forty-Nine Cases*

Findings	Adherent Pericarditis and Associated Cardiac Disease, Cases	Adherent Pericarditis Only, Cases
Auricular fibrillation	10	8
Auricular flutter	1	
Extrasystolic arrhythmia	3	1
Complete heart block	1	
Delayed auriculoventricular conduction	1	
Incomplete bundle branch block	1	1
Significant T wave negativity	11	9
Change in contour and elevation of R T segment	2	

Electrocardiograms were obtained in forty-nine cases (34 per cent). Auricular fibrillation was the most frequent disorder of rhythm, occurring in eighteen cases (table 5). In three other cases in which electrocardiographic study was not made, auricular fibrillation was present, making its incidence in the entire group 14.5 per cent. This figure may be less than the actual incidence, for it is possible that arrhythmia may not have been mentioned in some of the earlier cases in which it occurred. It occurred in eight (80 per cent) of the cases in which adherent pericarditis only was present. The other findings are tabulated according to their occurrence. The incidence of significant T wave negativity in the cases of adherent pericarditis unassociated with other cardiac disease was high. In four of these cases there was T wave negativity in all leads.

The amplitude of the deflections in thirty-eight cases was carefully studied, and in general there was a lowering of amplitude of both the R and the T waves.<sup>13</sup> In all cases in which measurements were carried

<sup>12</sup> Dieuaide, F. R. The Electrocardiogram as an Aid in the Diagnosis of Adhesive Pericardial Mediastinitis, *Arch Int Med* **35**: 362 (March) 1925.

<sup>13</sup> Normal amplitude of R wave = 10, 15 mm, T wave = 3, 8 mm.

out, the greatest diminution occurred in lead III. In cases in which obliteration of the pericardial cavity was partial, on the one hand, and cases in which it was complete, on the other, no appreciable differences in amplitude occurred. The average amplitude of the T waves was small in all leads. The figures were as follows: in lead I, 3.05 mm, in lead II, 3.25 mm, and in lead III, 2.86 mm. The R waves were similarly relatively low: the average in lead I was 7.15 mm, in lead II, 7.22 mm, and in lead III, 6.21 mm.

*Mode of Death*—The heart was directly concerned with the death of the patient in fifty-seven cases (39.5 per cent). The predominant syndrome was that of congestive cardiac failure, it was recorded in thirty-nine cases (68.4 per cent). In twelve cases, death occurred very suddenly, and among these were nine cases of coronary disease.

TABLE 6—*Comparison of Data in Cases in Which Death Was Caused by Heart Disease, with Those in Cases in Which It Was Caused by Other Conditions*

Predominant Cardiac Condition, in Addition to Adherent Pericarditis	Death from Cardiac Disease				Death from Other Causes			
	Cases	Per Cent	Average Cardiac Weight, Gm	Average Age, Yr	Cases	Per Cent	Average Cardiac Weight, Gm	Average Age, Yr
Rheumatic heart disease with mitral stenosis	19	76.0	489.6	31.6	6	24.0	435.0	53.5
Coronary sclerosis	16	51.6	719.9	57.0	15	48.4	451.7	60.0
Rheumatic heart disease with aortic insufficiency	6	100.0	891.0	27.6				
Aortic syphilis	4	100.0	550.0	56.5				
Hypertensive heart disease	2	18.1	700.0	56.5	9	81.9	535.8	52.7
No cardiac disease other than adherent pericarditis	10	14.9	619.0	43.7	57	85.1	367.0	48.6
Total and average	57	39.5	625.7	43.1	87	60.5	411.6	52.4

Detachment of mural thrombi resulting in fatal emboli occurred in four cases. Two patients died from subacute bacterial endocarditis (*Streptococcus viridans*).

Differences in data become evident when the essential findings in those cases in which patients died of heart disease are compared with those in cases in which the cause of death was unrelated to the heart (table 6).

The average weight of the heart among the patients who died of heart disease was 625.7 Gm, whereas in the group in which death was not related to heart disease, the cardiac weight was 411.6 Gm. The difference is 214.1 Gm. This appears to be important, and emphasizes the fact that the presence of a large heart is a significant prognostic sign. The average age of the patients who died from heart disease was 9.3 years less than that of the patients who died from other causes. The respective averages were 43.1 years as opposed to 52.4 years.

It is significant that 85.7 per cent of the patients with auricular fibrillation died of heart failure. Likewise, both the patients with

incomplete bundle branch block and those with complete heart block died as the result of heart failure

Causes of death that were not concerned with the heart were as follows: Carcinoma, twenty-four cases, pneumonia, eight, nephritis, sarcoma, empyema and pulmonary embolism, six each, pyelonephritis and peritonitis, five each, septicemia, tumor of the brain, pulmonary abscess and ulcerative colitis, two each, perforated peptic ulcer, adenomatous goiter with hyperthyroidism, intestinal obstruction, psychosis, meningitis, cerebral hemorrhage, pyemia, purpura hemorrhagica, pernicious anemia, hepatic cirrhosis, diabetes mellitus and Hodgkin's disease, one each

#### COMMENT

It becomes evident from this study that adherent pericarditis does not manifest its presence by a syndrome, nor by characteristic signs. The diagnosis of adherent pericarditis must be developed by composite analysis of symptoms and signs, each carefully considered and weighed in relation to the others.

Careful determination of etiologic factors demands considerable emphasis, and at times may be the only positive clue to identification of adherent pericarditis. The history of rheumatic fever should at once arouse suspicion, likewise the history of intrathoracic infection, healed cardiac infarction and intrathoracic cancer. The elicitation of symptoms indicative of previous pericarditis is, of course, almost positive evidence of partial obliteration of the pericardial cavity.

The presence of a large heart, in the absence of valvular lesions, of hypertension, of evidence of previous elevation of blood pressure, and of a clinical history that would indicate previous cardiac infarction, should at once suggest the possible existence of adherent pericarditis.

The presence of so-called classic signs of adherent pericarditis should receive full consideration, but their absence does not in any way justify failure to diagnose the disease. The presence of other cardiac disease does not minimize the probability of adherent pericarditis being present, in fact, it may frequently increase the probability of its existence. This is particularly true in rheumatic carditis. Only too often, identification of a cardiac lesion causes the examiner to believe that he has satisfactorily explained his patient's symptoms. This is detrimental to complete diagnosis, for it is almost the rule that cardiac lesions are multiple.

Fixation of the heart, as determined by physical examination and roentgenography, is important in identification of mediastinopericarditis and parietal adhesions. Unfortunately, so far as diagnosis is concerned, these cases are in the minority (8.3 per cent), and this sign fails completely in the majority of cases. The status is the same with regard to electrocardiography, fixation of the electrical axis is virtually confined

to the same group of cases. The presence of R and T waves of low amplitude in the electrocardiogram is suggestive of adherent pericarditis, but their occurrence in other diseases of the heart is well known and they cannot, therefore, be considered pathognomonic.

We wish particularly to stress the necessity for the development of a clinical sense of suspicion regarding the existence of adherent pericarditis in all cases of surmised or actual cardiac injury, and we are led to believe that adoption of such an attitude will distinctly decrease the large diagnostic error that prevails at the present time.

#### SUMMARY

One hundred and forty-four cases of adherent pericarditis in which the patients came to necropsy at the Mayo Clinic were studied with particular reference to clinical and pathologic correlation.

A marked predominance of the incidence in males occurred. Etiologic diseases occurred in the following order: (1) rheumatic fever, (2) intrathoracic infection, (3) cardiac infarction, (4) syphilis (certainly present, possibly etiologic) and (5) neoplastic invasion. The weights of the hearts were determined in 105 cases. The pericardium was partially calcified in fifteen cases (10.4 per cent).

Associated cardiac diseases occurred in seventy-seven cases (53.5 per cent). These in order of frequency were: (1) coronary sclerosis, (2) rheumatic heart disease with mitral stenosis, (3) hypertensive heart disease, (4) rheumatic heart disease with aortic insufficiency and (5) aortic syphilis.

The predominant clinical syndrome was referable to the heart in fifty-seven cases (39.5 per cent), and was in no manner related to the heart in eighty-seven cases (60.5 per cent). The latter comprised a miscellaneous group of diseases.

Death from heart disease occurred in 39.5 per cent of the cases, whereas the heart was not directly concerned with death in 60.5 per cent.

# PERICARDITIS

## II CALCIFICATION OF PERICARDIUM

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Calcification of the pericardium, also called "pericarditis calculosa," "concretio pericardii," "armored heart" and so forth, has been described by pathologists for many years. Scholz<sup>1</sup> mentioned that Morgagni published a report of a case of calcification of the myocardium in 1762, that Bordenave described a case in 1768, and that Simmons and Watson in 1783 published a report of a case, with an illustration. Schwartz,<sup>2</sup> in 1910, was probably the first to recognize this condition in the course of the life of the patient, he employed roentgenologic methods. Groedel<sup>3</sup> described a case in 1912 in which he made the diagnosis before death. A review of the literature by Case,<sup>4</sup> up to 1923, disclosed that in thirteen instances the condition had been recognized in the course of the life of the patient. Since Case's review, there have been reported in the literature twenty-one additional cases in which the diagnosis has been made in life,<sup>5</sup> a total of thirty-four cases so diagnosed,

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From the Section on Cardiology, the Mayo Clinic

1 Scholz, Thomas. Calcification of the Heart. Its Roentgenologic Demonstration. Review of Literature and Theories on Myocardial Calcification, Arch Int Med **34** 32 (July) 1924. Radiographic Demonstrations of Calcification of the Myocardium During Life, J Radiol **5** 131 (April) 1924.

2 Schwartz, Gottwald. Wien klin Wchnschr **23** 1823, 1910.

3 Groedel, F M. Erste Mitteilung uber die Differenzierung einzelner Herzhohlen im Rontgenbilde und den Nachweis von Kalkschatten in der Herzsilhouette intra Vitae, Fortschr a d Geb d Rontgenstrahlen **16** 337, 1911.

4 Case, J T. Pericarditis Calculosa. Report of New Case Discovered Roentgenologically, J A M A **80** 236 (Jan 27) 1923.

5 Arnesen, J. Case of Calcified Pericarditis (Panzerherz), Norsk mag f laegevidensk **88** 688 (Aug) 1927. Cutler, E C, and Sosman, M C. Calcification in Heart and Pericardium, Am J Roentgenol **12** 312 (Oct) 1924. Desplats, R, and d'Hour, H. Calcification du pericarde, J de radiol et d'electrol **13** 45 (Jan) 1929. Forman, F. Case of Calcification of the Pericardium, J M A South Africa **5** 271 (May 9) 1931. Guelke and Lommel. Herzbeutelresektion bei Concretio pericardii, Klin Wchnschr **4** 737 (April 16) 1925, abstr, J A M A **84** 1881 (June 13) 1925. Jones, H W, and Roberts, R E. Calcification of the Pericardium, Brit J Radiol **32** 167 (May) 1927. Lawen, A, and Matthes, M

and, as will be seen we have one such case to add. Ninety-four cases of calcification of the pericardium in which necropsy was performed were reported in the literature, up to 1924.

The present study is drawn from the following material: fifteen cases in which the presence of calcification of the pericardium was proved at necropsy, and one case in which it was proved clinically. In addition, four cases are mentioned in which there was clinical evidence of calcification of the pericardium, but in which its presence was not proved. Among the fifteen subjects who came to necropsy, twelve were males and three, females. The youngest subject was 24 years of age, and the oldest, 84. The average age was 48.6 years.

#### PATHOLOGIC DATA

Chronic adherent pericarditis was present in all fifteen cases in which necropsy was performed. These were the only cases of calcification of the pericardium in 144 cases of chronic adherent pericarditis found in the course of 8,912 postmortem examinations. This is a somewhat higher incidence than that found by Wells,<sup>6</sup> he found four cases of calcification in 128 cases of adherent pericarditis, in 1,000 postmortem examinations. Chronic mitral endocarditis was present in four instances. Aortic and mitral endocarditis, aortic, mitral and tricuspid endocarditis,

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Ein weiterer Fall von erfolgreich operierter Concretio pericardii, *Deutsche med Wchnschr* **54** 617 (April 13) 1928. LeGoff, Calcification du pericarde, *Bull et mem Soc de radiol med de France* **15** 329 (Dec) 1927. Lenker, J. L. Pericarditis calcuosa, *Pennsylvania M J* **34** 89 (Nov) 1930. Lossen, Heinz, and Kahl, Hermann. Ein Fall von Panzerherz, *Zentralbl f Chir* **51** 2585 (Nov 22) 1924. Pareja, J. M. Algunas consideraciones clinicas con respecto a una observación de pericarditis callosa, *Rev med latino-am* **16** 519 (Jan) 1931. Ramey, C. W. Calcified Pericardium Occurring in a Patient with Peptic Ulcer, *M J & Rec* **122** 212 (Aug 19) 1925. Reed, C. O. Calcification of the Pericardium, *U S Vet Bur M Bull* **4** 263 (March) 1928. Rusconi, M. Un caso di pericarditis calcuosa, *Cuore e circolaz* **11** 485 (Dec) 1927. Schlesinger, Hermann. Das Panzerherz, *Med Klin* **22** 11 (Jan 2) 1926. Starck, Hugo. Zur Pathologie des Panzerherzens, *ibid* **24** 1736 (Nov 9) 1928. Stone, W. J. Adherent Pericardium with Calcification, *Am Heart J* **1** 434 (April) 1926. Turner, H. H. Calcification of the Pericardium. Report of Three New Cases with Review of the Literature, *Internat Clin* **4** 137 (Dec) 1924. Vilvandre, G. E. A Case of Calcification of the Pericardium, *Lancet* **1** 564 (March 15) 1930. Wells, H. G. The Pathology of the Healed Fibrous Adhesions of the Pericardium, *Am J M Sc* **123** 241 (Feb) 1902. Youmans, J. B. Calcification of the Pericardium, a Clinical Problem, with Report of Two Additional Cases Diagnosed During Life, *Ann Clin Med* **4** 1032 (June) 1926. Youmans, J. B., and Merrill, E. F. Calcification of Pericardium. Report of Case Discovered Roentgenologically During Life, *J A M A* **82** 1833 (June 7) 1924.

6 Wells, H. G. *Chemical Pathology*, ed 5, Philadelphia, W. B. Saunders Company, 1925.

syphilitic aortitis with aortic insufficiency, and coronary thrombosis with cardiac infarction occurred in one instance each

The weight of the heart was recorded in twelve instances, and the average cardiac weight was 584 Gm. In two cases, the hearts were apparently of normal size. The pericardial sac was completely obliterated in eight instances and partially obliterated in seven.

Chronic pleuritis was present in four instances, hydrothorax in four, pulmonary infarction in two, and pyothorax in one. Evidence of tuberculosis was not present in a single case of the fifteen. In only four instances was there any significant pathologic change in the liver. In one of these, there was pigmentary cirrhosis of the liver; this was a case of hemochromatosis. In two cases there was "atrophic cirrhosis," and in one chronic passive congestion of the liver.



Fig 1 (case 1 of the fifteen summarized) —Anterior aspect of the heart. The calcified pericardium is partially separated from the heart.

The degree of calcification varied from involvement of a few areas to involvement of the entire pericardium, with the exception of a small portion at the apex. This extreme condition was present in case 1 (figs 1 and 2). In case 2, the pericardium was calcified moderately throughout, except at the apex. In case 3, the pericardium was calcified throughout, except a small area over the posterior surface of the right auricle. A brown, inspissated mass of old blood was partially calcified. Two mitral cusps contained rather marked deposits of calcium. In case 4, there were large, calcareous plaques over the right auricle and right ventricle. The aortic and mitral leaflets contained calcareous deposits. In case 5, there was a circumferential band of calcareous material in fibrous adhesions, just above the base of the heart. In case 6, there was extensive calcification posteriorly, one plaque measured 4 cm. in diameter. In case 7, there was an area of calcification on the posterior and

lateral surface of the left auricle, it measured 2 by 4 cm, and was 2 mm thick. In case 8, there were calcified adhesions between the apex and the pericardial sac, and calcified areas on the anterior and posterior surfaces. In case 9, numerous calcified areas 1 by 3 cm in diameter were found on the anterior surface of the ventricles. In case 10, fibrous adhesions with areas of calcification were present. In case 11, there



Fig 2 (case 1 of the fifteen summarized) —Postmortem roentgenogram of the heart. Calcification is generally distributed.

were numerous areas of calcification in the pericardial adhesions and calcification in leaflets of the mitral valve, the chordae tendineae, also, were calcified. In case 12, adhesive pericarditis with areas of calcification was seen. In case 13, there were calcified areas in the superior and right aspects of the pericardium, one of which was 5 cm in diameter and 5 mm thick. In case 14, there was a calcified mass, 1 by 2 cm in diameter, on the upper portion of the pericardium, reflected onto the



pulmonary artery In case 15, there were several calcified areas on the right ventricle, each about 12 by 7 mm in diameter

There were several instances in which there was deposition of calcium in regions other than the pericardium in three of these, marked deposits of calcium were found in the mitral valve, in one, in the aortic valve, and in one, in both the aortic and mitral valves In one case, there were numerous gallstones, multiple calculi in the pancreatic ducts and multiple plaques in the diaphragm Stones previously had been removed from the urinary bladder in one case Marked coronary sclerosis occurred in two instances and excessive aortic sclerosis once

#### CLINICAL DATA

Roentgenograms of the thorax had been made in five of the cases in which necropsy was performed In three of these instances, the heart was reported to be moderately enlarged and in one, greatly enlarged, and in one the transverse diameter of the cardiac shadow was 18.5 cm But in none of these fifteen cases was calcification of the pericardium recognized prior to necropsy

In five of the fifteen cases, electrocardiographic studies were made Auricular fibrillation was present in three cases, and significant changes in the T wave, in two Ascites was present in four cases, in two of which it was present in marked degree, and in two, in moderate amount

There were ten cases in which failure of the heart was the primary cause of death The death of five patients was due to causes other than cardiac failure

The diagnoses relative to the heart in eight cases were chronic adhesive pericarditis, myocardial disease with cardiac failure, myocardial insufficiency, cardiac failure and syphilitic aortitis with aortic insufficiency, each in one case, and chronic rheumatic mitral endocarditis with mitral stenosis and insufficiency in three cases The clinical diagnoses in the other seven cases were bronze diabetes, carcinoma of the stomach, perforation of gastric ulcer, cirrhosis of the liver carcinoma of the jejunum, perforation of the rectosigmoid and pyelonephritis

In six of the fifteen cases there was a fairly definite history of rheumatic fever and in one case syphilitic infection was present

As has been said (paragraph 2), there were four cases in which there was clinical evidence of calcification of the pericardium, but in which it was not proved Evidence of calcification was found only incidentally The patients had no symptoms that were referable to the heart Two of them had chronic infectious arthritis, one, carcinoma of the colon, and one, chronic cholecystitis with stones In one of the cases, roentgenologic examination revealed chronic bronchitis and fibrosis, and calcification of the margin of the pericardium, in one,

infiltration of the bases of both lungs and calcification of the left side of the pericardium. In one, a linear shadow of the left border of the heart, probably caused by calcification of the pericardium, and in one, bilateral tuberculosis with a small cavity and calcification of the left border of the pericardium.

In paragraph 2, we stated that in one of our cases calcification of the pericardium was proved in life. This case will now be reported in detail.

#### REPORT OF CASE

A man, aged 45, came to the Mayo Clinic in August, 1929. He had nothing of medical significance to tell regarding his blood relatives. He had been married eighteen years, but his wife had not been pregnant. When he was 8 years of age, he had scarlet fever. In 1907, he was examined for postal service and was told that his heart was "not quite all right." He had influenza in 1918, underwent operation for hydrocele in 1921, and had influenza again in 1921. However, his general health was good until eight years before he came to the clinic, at that time, his ankles and legs began to swell. Soon after the onset of these symptoms, he noticed some dyspnea on climbing stairs and on severe exertion. These symptoms gradually increased in severity. In the few years before we saw him, he had an occasional pain in the lower left part of the thorax. He had experienced some palpitation. In the few months before his registration, he gained in weight. He had been able to continue his work in a bank.

Examination disclosed that the patient was well developed and well nourished. The blood pressure was 110 mm of mercury systolic and 70 diastolic. The pulse rate was 100 beats each minute, and was totally irregular. The temperature was 98 F. Moderate dyspnea and considerable cyanosis were present. The veins in the neck were distended. Broadbent's sign was present. There was marked passive congestion at the bases of both lungs. Ascites was marked, and there was edema of the lower extremities. Cardiac dullness was slightly increased. Heart tones were distant, of poor quality and totally irregular.

Urinalysis gave essentially negative results. The concentration of hemoglobin and the number of erythrocytes were slightly less than normal. The Wassermann reaction of the blood was negative.

Roentgenologic examination (fig 3A) gave evidence of old empyema of the lower right portion of the thorax, with rather marked retraction of the lower part of the right lung, with some pleuritic adhesions. The electrocardiogram disclosed that the cardiac rate was 74, and that auricular fibrillation was present. The Q-R-S complex was slurred in lead II and notched in lead III, there was evidence of slight right ventricular preponderance, and the T wave in derivation III was inverted. A diagnosis was made of chronic adhesive pericarditis, with congestive cardiac failure. The patient was placed in the hospital under a regimen for congestive cardiac failure, and abdominal paracentesis was done, 15,000 cc of straw-colored fluid was removed. Ammonium nitrate and salyrgan, and digitalis, were administered to bring about diuresis, and the patient was dismissed from the hospital twenty-two days after his admission, greatly improved.

The second admission of the patient was in 1930, one year after the first. The findings were about the same as they were on his previous admission, except that congestive failure was more marked, and the heart was more greatly hypertrophied.

(fig 3 *B*) He was again placed in the hospital, on the same treatment as before. He underwent another abdominal paracentesis, and this time 11,000 cc of straw-colored fluid was removed. He was dismissed thirteen days after admission, practically free from fluid, and his condition again was greatly improved.

The third admission was in 1931, one year after the second visit. In the interim, the patient had undergone abdominal paracentesis twice, 14,000 cc of fluid was withdrawn one time, and 16,000 cc another time. The patient's condition at this time was worse than it had been at any previous admission. The findings were essentially the same, but congestive failure was more marked, and roentgenologic examination of the thorax and especially of the heart (fig 3 *C*) gave evidence of extensive calcification of the pericardium that had not been recognized on previous admissions. The patient was dismissed eleven days after admission, but with only moderate improvement.



Fig 3 (case reported in detail) —*A*, roentgenogram taken in August, 1929, there is a small area of calcification along the left border of the pericardium, *B*, roentgenogram taken in August, 1930, the area of calcification is larger, *C*, roentgenogram taken in August, 1931, calcification is extensive.

#### COMMENT

Wells found the composition of calcified material to be nearly constant regardless of where the material is formed in the body. He found the composition to be 86 per cent calcium phosphate, 13 per cent calcium carbonate and 1 per cent magnesium phosphate. Barr<sup>7</sup> found deposits of calcium to be affected by a large number of factors, such as diminished blood supply, formation of necrotic tissue, degree of alkalinity of blood and tissues, the amounts of calcium and phosphates in the body, concentration of the blood, and presence and amount of vitamin C and of parathyroid hormone.

<sup>7</sup> Barr, D. P. Pathological Calcification, *J. Missouri M. A.* **27**: 593 (Dec) 1930.

Hewitt<sup>8</sup> has called our attention to the story of "Ethan Brand" by Nathaniel Hawthorne, which contains a vivid description of the death of the main character, who had a "heart of stone." The description is so vivid that one wonders if Hawthorne knew of a case. If not, it would be interesting to know the source of the tale. We feel that the story is so unique and so relevant that part of it is well worth quoting.

"With his long pole in his hand, he (Bartiam) ascended to the top of the kiln. After a moment's pause, he called to his son

"'Come up here, Joe!' he said

"So little Joe ran up the hillock, and stood by his father's side. The marble was all burnt into perfect snow-white lime. But on its surface, in the midst of the circle, snow-white too, and thoroughly converted into lime, lay a human skeleton, in the attitude of a person who, after long toil, lies down to long repose. Within the ribs, strange to say—was the shape of a human heart.

"'Was the fellow's heart made of marble?' cried Bartiam, in some perplexity at this phenomenon.

"'At any rate, it is burnt into what looks like special good lime, and, taking all the bones together, my kiln is half a bushel the richer for him.'

"So saying, the rude lime-burner lifted his pole, and, letting it fall upon the skeleton, the relics of Ethan Brand were crumbled into fragments."

#### SUMMARY AND CONCLUSIONS

Sixteen proved cases of calcification of the pericardium are considered, in fifteen of these cases, the diagnosis was established at necropsy, and in one case, in life. All of the sixteen patients had extensive chronic adhesive pericarditis. The diagnosis made in life was accomplished by roentgenologic examinations. Four other clinical cases are described, but the findings were not sufficiently striking for them to be classified as proved cases. The single etiologic factor that affected the largest number of patients was rheumatic infection. Tuberculosis was not present in any one of the proved cases, it was present in one of the four unproved cases. It would appear that calcification of the pericardium is a sequel of extensive chronic adhesive pericarditis and is an end-result of the same inflammatory process that produces chronic adhesive pericarditis. It is not a common condition, for it was found in only 15 of 144 cases of chronic adherent pericarditis found in the course of 8,912 postmortem examinations. Recognition of deposits of calcium in the pericardium by means of roentgen rays may be an aid in making the diagnosis of chronic adhesive pericarditis, which condition is extremely difficult to recognize.

<sup>8</sup> Hewitt, R. M. Nathaniel Hawthorne's Report of a Case of Pericarditis Calculosa, J. A. M. A. 98:68 (Jan. 2) 1932.

# PERICARDITIS

## III PERICARDITIS WITH EFFUSION

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Under normal conditions, the pericardial sac contains a small amount of fluid, varying in quantity from 10 to 50 cc. The fluid is clear and light amber in color. In the presence of disease of the pericardium, or of congestive heart failure, the pericardial fluid may become altered in character and increased in amount. The alterations in the organism in cases of pericarditis with effusion are of one, or both, of two sorts: (1) a mechanical handicap is imposed on the heart by the presence of considerable fluid, and (2) if the effusion is the result of pericardial infection, there is sepsis or toxemia.

Pericardial effusion frequently is not recognized in life, and it has been stated that amounts of less than 150 cc. usually defy detection. This is, of course, not difficult to understand when one realizes the opportunity for concealment of fluid in the pericardial sac, if obstructing, adhesive processes are absent. The tendency for fluid to gravitate occurs here, as elsewhere, and therefore the fluid changes its position, depending on the patient's posture. Even moderate excess of fluid may be concealed when the patient is recumbent, because it gravitates to the posterior portion of the sac. When fluid is present in an amount completely to fill and distend the pericardium, its recognition is usually not difficult.

### MATERIAL

Cases in which the amount of pericardial fluid was more than normal, or in which the fluid, irrespective of its amount, was altered in character, were selected for this study. There were 113 such cases, or 30 per cent of the cases of pericarditis in which necropsy was performed at the Mayo Clinic. The cases were grouped in the following manner: acute purulent pericarditis, seventy-seven cases (68.1 per cent of all cases of pericarditis with effusion), fibinous pericarditis with effusion, thirty cases (26.5 per cent), tuberculous pericarditis, three cases (2.7 per cent), and noninflammatory effusion, three cases (2.7 per cent).

The predominance of the incidence in males was similar to that noted in the study of adherent pericarditis. Seventy-eight of the cases

occurred in males (69 per cent) and thirty-five in females (31 per cent). The patients represented practically all the decades of life. The youngest patient was aged only 8 months, whereas the oldest patient was aged 89 years. The average age was 43.5 years. The majority of the patients (72.5 per cent) were between the ages of 30 and 70 years.

#### ETIOLOGY

In considering the etiology of pericarditis with effusion, it is necessary to take up the cases in groups corresponding to the classifications given in the second paragraph preceding.

*Acute Purulent Pericarditis*—Septic processes were the basis of purulent pericarditis in all of the seventy-seven cases. Intrathoracic infectious disease was apparently the primary condition in fifty-seven cases (74 per cent of the cases of acute purulent pericarditis), whereas sepsis elsewhere in the body occurred in twenty cases (26 per cent).

Thoracic empyema occurred with greatest frequency. It was present in twenty-eight cases, and was associated with bronchopneumonia in eleven cases and with lobar pneumonia in two. Bronchopneumonia without empyema occurred in ten cases, acute nontuberculous pleuritis in five, and multiple pulmonary abscesses and mediastinitis each in four cases. Other conditions which occurred less frequently were abscess of the liver with rupture into the pericardium in two cases, one of which was due to actinomycosis, pulmonary emboli with necrosis and infection in two cases, hepatic abscess with suppurative cholangitis and thoracic extension, and carcinoma of the lung with abscess, in one case each. The remaining twenty cases resulted from remote sepsis, and included such diseases as gangrenous appendicitis with rupture, puerperal endometritis, scarlet fever, abscess of the brain and so forth.

*Fibrous Pericarditis with Effusion*—These thirty cases were characterized by the presence of nonpurulent fluid in excessive amounts, or by normal amounts of fluid of altered character. This group, to a large extent, represented cases of secondary nonpurulent pericarditis. Here, again, intrathoracic infectious disease predominated. It was present in twenty-one cases (70 per cent of the cases of fibrous pericarditis with effusion). Acute, nontuberculous pleuritis, which occurred in twelve cases, was the outstanding etiologic disease. Bronchopneumonia occurred in three cases and mediastinitis in two cases. Thoracic empyema occurred in three cases and was associated with bronchopneumonia and with lobar pneumonia in two of them. Aneurysmal erosion of the trachea, with inflammatory extension, was found in one case. Primary fibrous pericarditis with effusion occurred in only nine cases (30 per cent).

*Tuberculous Pericarditis with Effusion*—Only three cases of this condition were recorded. All were associated with tuberculosis of other portions of the body. A tuberculous abscess of the left suprarenal gland occurred in one case, pulmonary tuberculosis in one, and miliary tuberculosis in one.

*Noninflammatory Effusion*—There were only three cases in this class. Two of the patients died of congestive heart failure, one had adherent pericarditis, the other, coronary disease. The third patient died as the result of pyelonephritis. The infrequent occurrence of this form of effusion may be explained, in part, by the effective modern treatment of edema by means of mercurial diuretics and ammonium nitrate. In the vast majority of instances, the retained fluid is readily excreted, and when death eventually occurs from heart failure, the serous cavities are relatively dry.

#### PATHOLOGIC DATA

Records of the weights of sixty of the hearts (53 per cent) of the entire series of 113 cases of pericarditis with effusion were suitable for pathologic study. In a number of cases such study could not be made in some of these there were unusual cardiac weights, such as are met with in study of infants and small children, and in a few cases, the recorded weights included those of the entire pericardium.

Regardless of pathologic grouping, the weights of the hearts were as follows: between 100 and 199 Gm in one case (17 per cent of sixty), 200 and 299 Gm in eight cases (13.3 per cent), 300 and 399 Gm in twenty-two cases (36.7 per cent), 400 and 499 Gm in thirteen cases (21.7 per cent), 500 and 599 Gm in eleven cases (18.3 per cent), 600 and 699 Gm in four cases (6.6 per cent), and 700 and 799 Gm in one case (1.7 per cent). The average cardiac weight was 426.8 Gm. In fifty-one cases (85 per cent of sixty) the cardiac weights were definitely in excess of normal, according to the standard of Smith<sup>1</sup>. He found that the average weight of normal hearts of adult males was 294 Gm, and that the average weight of normal hearts of adult females was 250 Gm. Cardiac weights in excess of 500 Gm were found in sixteen cases. The heart of a small woman, 42 years of age, who had exophthalmic goiter weighed only 130 Gm. The greatest recorded weight was 750 Gm, the patient was a man, 52 years of age, who had hypertension.

In analyzing the cases according to pathologic groups, certain differences in average cardiac weight appeared. The average weight of the

<sup>1</sup> Smith, H. L. The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age, *Am Heart J* 4:79 (Oct) 1928.

hearts in the thirty-seven cases of purulent pericarditis in which the weights were known was 392.1 Gm. In this group, also, the majority of the cases (86.4 per cent) presented cardiac weights in excess of 300 Gm. The minimal cardiac weight was 130 Gm, whereas the maximal weight was 750 Gm. The weights of the hearts were between 100 and 199 Gm in one case (2.7 per cent of thirty-seven), from 200 to 299 Gm in five cases (13.5 per cent), from 300 to 399 Gm in fifteen cases (40.5 per cent), from 400 to 499 Gm in eleven cases (29.7 per cent), from 500 to 599 Gm in three cases (8.2 per cent), between 600 and 699 Gm in one case, and between 700 and 799 Gm in one case (2.7 per cent respectively).

In nineteen cases of fibinous pericarditis with effusion in which the cardiac weights were computed, the average weight was 454.4 Gm, 62.3 Gm greater than in the cases of purulent pericarditis. In this group, again, the weight of most of the hearts (94.7 per cent) exceeded 300 Gm. The smallest recorded cardiac weight was 253 Gm, and the greatest, 650 Gm. In detail, the weights were from 200 to 299 Gm in two cases (10.5 per cent of nineteen), from 300 to 399 Gm in six cases (31.6 per cent), from 400 to 499 Gm in two cases (10.5 per cent), from 500 to 599 Gm in six cases (31.6 per cent), and from 600 to 699 Gm in three cases (15.8 per cent).

The weight of the heart in the only case of tuberculous pericarditis in which it was recorded was 250 Gm. The heart was increased in weight in all the cases of noninflammatory effusion, the average weight was 466.6 Gm. The weights were 300, 525 and 575 Gm, respectively.

These analyses do not exclude primary cardiac disease, which when present contributes to cardiac hypertrophy. Further subdivisions are considered later in this study. Musser and Herrmann,<sup>2</sup> in their group of seventeen cases, comprising cases of acute and subacute serofibinous or hemorrhagic pericarditis, found the average cardiac weight to be 363.2 Gm.

#### ASSOCIATED CARDIAC DISEASE

Other disease of the heart was associated with the pericarditis in only thirty-three cases (29.2 per cent of the 113 cases in the whole series). The incidence of associated disease was much smaller than that which was found in our study of adherent pericarditis.

In the present study of pericarditis with effusion, hypertensive heart disease occurred with greatest frequency among associated diseases, there were ten cases (8.8 per cent of the entire group of 113 cases). The average weight of the heart was 570.5 Gm, the minimal weight was 415 Gm and the maximal weight, 650 Gm. Purulent pericarditis

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<sup>2</sup> Musser, J. H., and Herrmann, G. R. Chronic Pericarditis. The Clinical and Experimental Aspects, *J. A. M. A.* **87**: 459 (Aug. 14) 1926.



and fibrinous pericarditis with effusion were of equal occurrence among these ten cases. The average age of the patients was 48 years. The youngest patient was 26 years of age, and the oldest, 59.

Rheumatic heart disease occurred next in frequency, eight cases were recorded (7.1 per cent of 113). The lesions, and their frequency, were as follows: mitral stenosis, three cases, aortic insufficiency, two cases, mitral stenosis and aortic insufficiency, one case, mitral stenosis and tricuspid insufficiency, one case. The average cardiac weight was 548.3 Gm. The smallest heart weighed 466 Gm, the largest, 745 Gm. Purulent pericarditis occurred in six of these eight cases and fibrinous pericarditis with effusion in two cases. The average age of the patients was 41.5 years, the youngest patient was 10 years of age, and the oldest, 59.

Coronary sclerosis occurred in eight cases (7.1 per cent of 113). Acute cardiac infarction was noticed in three of these cases, in two cases, the infarction was the result of thrombosis, and in one, of embolism. Healed infarction was found in one case. Five cases presented evidence of previous or existent hypertension. The average cardiac weight was 538 Gm, the minimal weight was 350 Gm, and the maximal weight, 750 Gm. The values in this group are undoubtedly increased by the influence of associated hypertension, although the degree of coronary sclerosis was so marked as to necessitate their inclusion in this classification. The pericarditis was of the purulent type in four cases, of the fibrinous type with effusion in two cases, and of the noninflammatory type with effusion, also in two cases. The average age of the patients was 58.6 years. The youngest patient was aged 48 years, and the oldest patient, 80 years.

Acute bacterial endocarditis occurred in five cases (4.4 per cent of 113). It was but an incident in septicemia in all of them. The average cardiac weight was 397.5 Gm, the minimal weight was 325 Gm, and the maximal weight, 470 Gm. The pericarditis was of the purulent type in three cases, and of the fibrinous type, with effusion, in two cases. The average age was 49 years. The youngest patient was only 13 years of age, whereas the oldest was 67.

What was apparently an example of the heart in hyperthyroidism occurred in a man, 26 years of age, who had a hyperfunctioning adenomatous goiter. There was no evidence of preexistent hypertension, and the valves of the heart were normal. The heart weighed 525 Gm, and fibrinous pericarditis with effusion was present.

The remaining patient of the thirty-three who had cardiac disease associated with the pericarditis was a man, aged 62, who suffered from syphilitic aortitis, and who had a large saccular aneurysm of the innominate artery, with erosion and perforation of the trachea. The

pericarditis was of the fibrinous type with effusion. The weight of the heart was not recorded.

There were eighty cases (70.8 per cent of 113) of pericarditis unassociated with other cardiac disease. The average cardiac weight was 351 Gm., and was, as would be anticipated in this group, considerably less than that of any component of the group in which other cardiac disease was associated with pericarditis. Moreover, 351 Gm. is less than the average weight of the heart (537.8 Gm.) in all cases in which there was associated cardiac disease. In these eighty cases, the pericarditis was of the purulent type in fifty-nine, of the fibrinous type in seventeen, of the tuberculous type in three, and of the noninflammatory type in one. The average age of the patients was 52.2 years, three and a half years greater than that of patients who had cardiac disease associated with the pericarditis. The youngest patient was 8 months of age, the oldest, 85 years.

The weight of the hearts of twenty-six patients with purulent pericarditis was known. In one case (3.9 per cent of twenty-six) the cardiac weight was between 100 and 199 Gm., in five cases (19.2 per cent), from 200 to 299 Gm., in thirteen cases (50 per cent), from 300 to 399 Gm., and in seven cases (26.9 per cent), from 400 to 499 Gm., the average weight was 348 Gm. Of eight cases of fibrinous pericarditis with effusion in which the cardiac weight was known, in one case (12.5 per cent of eight) the weight was between 200 and 299 Gm., in four cases (50 per cent), from 300 to 399 Gm., in two cases (25 per cent), from 400 to 499 Gm., and in one case (12.5 per cent), from 500 to 599 Gm., the average weight was 379.7 Gm. In one case of tuberculous pericarditis, the cardiac weight was 250 Gm., and in one case of non-inflammatory effusion, 300 Gm.

#### PERICARDIAL FLUID

Among the seventy-seven cases of purulent pericarditis in the series, the pericardial content was recorded in forty-one cases (53.2 per cent). The average content was 171.2 cc. The smallest amount was 10 cc. and the greatest, 750 cc. The amount of effusion present in the thirty cases of fibrinous pericarditis in the series was recorded in twenty-six cases (86.6 per cent). The average content was slightly greater than that in the cases with purulent pericarditis, 195.1 cc. The smallest amount of effusion was 25 cc., the greatest, 500 cc. The pericardial content in the one case of tuberculous pericarditis in which it was determined was 1,500 cc. This quantity of fluid was aspirated a few days before death. The average pericardial content in the cases of noninflammatory effusion was 100 cc. The minimal quantity was 50 cc., the maximal quantity, 150 cc.

## ASSOCIATED PLEURAL FLUID

In eighty-three cases (73.5 per cent of 113) there was fluid in one or both pleural cavities. In the cases of purulent pericarditis, pleural fluid occurred in 81.8 per cent. The right pleural cavity contained fluid in twenty of these cases of purulent pericarditis, the left, in fourteen cases, and both pleural cavities, in twenty-nine cases. The average amount of fluid was 570.1 cc, the smallest amount was 75 cc, and the greatest, 1,500 cc. Pleural fluid was present in 67 per cent of the cases of fibinous pericarditis with effusion. The right pleural cavity contained fluid in eight of these cases, the left, in three, and fluid was present in both cavities in nine cases. The average content was 475 cc, the smallest amount was 75 cc, and the greatest, 1,500 cc. Two patients with tuberculous pericarditis had pleural fluid. In both instances, the deposition was bilateral. The amount, in the one case in which it was recorded, was 150 cc in each pleural cavity. In all cases of noninflammatory pericardial effusion there was hydrothorax. The distribution was unilateral in two cases and bilateral in one. The average content was 625 cc, the minimal quantity was 100 cc, and the maximal, 1,200 cc.

## CLINICAL FEATURES

Only fifteen patients (13.2 per cent of the entire 113 in the series) presented symptoms and signs predominantly of cardiac disease. Five cases in which pericarditis was of the purulent type included three cases of rheumatic heart disease, one case of coronary thrombosis and one case of coronary sclerosis. Among the patients with fibinous pericarditis with effusion, associated cardiac disease was the dominant condition in seven. These comprised three with coronary sclerosis, two with rheumatic heart disease and two with hypertensive heart disease. In only one patient with tuberculous pericarditis were the cardiac features emphasized, there was an enormous effusion in this case. In two of the cases of noninflammatory effusion, the dominant clinical picture was that of congestive heart failure, one patient had adherent pericarditis, and the other, coronary sclerosis.

The cases represented a great variety of diseases. The predominant clinical observations in the seventy-seven cases of purulent pericarditis were as follows: carcinoma, in fourteen cases, hyperfunctioning adenomatous goiter and peptic ulcer, each in five cases, bronchopneumonia, benign prostatic hypertrophy, nephritis and exophthalmic goiter, each in four cases, abscess of the liver and rheumatic heart disease, each in three cases, lobar pneumonia, empyema, abscess of the lung, acute bacterial endocarditis, influenza, cholecystitis and appendicitis (ruptured), each in two cases, and trifacial neuralgia, Addison's disease, scarlet fever, puerperal endometritis, cicatricial stenosis of the common bile

duct, myelogenous leukemia, uterine fibromyoma, pyonephrosis, lacerated perineum, endothelioma of the dura, coronary thrombosis, coronary sclerosis, fracture of femur, pleuritis, miliary tuberculosis, hepatic cirrhosis and multiple abscesses of the brain, each in one case

The predominant clinical observations in the thirty cases of fibrinous pericarditis with effusion were as follows carcinoma and coronary sclerosis, each in three cases, rheumatic heart disease, malignant hypertension, acute bacterial endocarditis and nephritis, each in two cases, and abscess of the liver, hypertensive heart disease, peptic ulcer, diabetes mellitus, osteomyelitis of the femur, acute pleuritis, appendicitis (ruptured), hyperfunctioning adenomatous goiter, influenza, exophthalmic goiter, infectious arthritis, empyema, hernia, nephrolithiasis, syphilitic aortitis and bronchopneumonia, each in one case

#### BLOOD PRESSURE

In considering the effect of pericardial effusion on blood pressure we included only those cases in which the pericardial content equalled or exceeded 150 cc. When the cases in which there were hypertension and aortic insufficiency had been excluded, twenty-three cases were available. The average readings of blood pressure were systolic, 121.8 mm, diastolic, 70.2 mm, and pulse pressure, 51.6 mm. When the averages of blood pressure are considered according to pericardial content, a slight correlation is evident although the number of cases is too small to permit definite conclusions to be drawn. In cases in which the pericardial content ranged from 150 to 199 cc, the average readings of blood pressure were systolic, 134.5 mm, diastolic, 67.8 mm, and pulse pressure, 66.7 mm. In cases in which the pericardial fluid was present in amounts varying from 200 to 299 cc, the average values for blood pressure were systolic, 124.5 mm, diastolic, 78 mm, and pulse pressure, 46.5 mm. In cases in which the pericardial fluid was present in amounts of from 300 to 399 cc, the average readings were systolic, 114 mm, diastolic, 64.3 mm, and pulse pressure, 49.7 mm. In cases in which pericardial fluid was in the amount of from 600 to 650 cc, average readings were systolic, 110 mm, diastolic, 71 mm, and pulse pressure, 39 mm. In cases in which pericardial fluid was present in amounts ranging from 700 to 750 cc, the average values were systolic, 103.5 mm, diastolic, 59 mm, and pulse pressure, 44.5 mm.

The average systolic pressure appears to drop in proportion to the amount of pericardial fluid present, and although the average pulse pressure tends to follow, the average diastolic values appear to fluctuate considerably.

#### SIGNS OF PERICARDIAL EFFUSION

Signs said to be characteristic of pericardial effusion are only infrequently encountered. As previously stated, it is impossible to deter-

mine the presence of less than 150 cc of excess fluid. Probably the most reliable sign of effusion is the size and contour of the heart as determined by roentgenogram, particularly when considerable excess fluid has accumulated. It consists of bulging at the lower angles of the cardiac shadow, the region to which fluid gravitates, and as more fluid accumulates the grooves of the heart and great vessels become filled, giving a rounded shadow. The characteristic delineations of the normal heart are obliterated. This results in the so-called "water-bottle" shadow.

Pericardial rubs are frequently present in the early stages, but become obliterated when the pericardial surfaces become separated by the increasing quantity of fluid. Distant and muffled heart tones are suggestive of pericardial effusion, but their presence in greatly dilated hearts is well appreciated. Diminution or obliteration of the apex beat is suggestive of pericardial effusion.

Enlargement of the liver with local tenderness, has been given as an early sign of pericardial effusion resulting from impingement on the orifices of the hepatic veins, which enter into the inferior vena cava. However, a tender, enlarged liver is the rule in congestive heart failure regardless of its type, and thus this sign becomes of minimal value so far as pericardial effusion is concerned.

Compression of the left lung (Ewart's<sup>3</sup> sign), occurring with extensive pericardial effusion, has been emphasized and although important and worthy of consideration when present, occurs also with enormously enlarged hearts. Enormous effusions occasionally cause compression of the esophagus and trachea producing dysphagia and respiratory obstruction.

Roentgenograms were obtained in thirty-four cases (30 per cent) and of these, nineteen gave evidence of varying degrees of cardiac enlargement. However, in only five cases was the shadow of the heart suggestive of effusion.

The electrocardiograms in twenty-four cases were available for study. Auricular fibrillation occurred in only four cases, in three of which there was associated cardiac disease. Auricular flutter occurred but once, there was associated cardiac disease in this case. Ten patients had significant T wave negativity, and eight of these had associated cardiac disease. Extrasystolic arrhythmia was present in five cases, in all of which there was associated cardiac disease.

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3 Ewart, William. Practical Aids in the Diagnosis of Pericardial Effusion, in Connection with the Question as to Surgical Treatment, *Brit M J* 1 717 (March 21) 1896.

## MODE OF DEATH

Death wholly as the result of cardiac disease was observed in only ten cases (88 per cent), of which two were cases of purulent pericarditis, six were cases of fibrinous pericarditis with effusion, and two were cases of noninflammatory effusion. Eighty-eight (77.9 per cent) of the patients died from sepsis. These cases comprised a miscellaneous group of conditions already discussed. Purulent pericarditis occurred in seventy-five cases and fibrinous pericarditis with effusion in thirteen cases. Death from other causes, such as hepatic cirrhosis, nephritis, pulmonary embolism, tuberculosis, and so forth, occurred in fifteen cases (13.3 per cent). In this group of fifteen were eleven cases of fibrinous pericarditis with effusion, three cases of tuberculous pericarditis and one case of noninflammatory effusion.

*Summary of Causes of Death in the One Hundred and Thirteen Cases*

Classification	Incidence of Given Causes of Death					
	Cardiac Disease		Sepsis		Other Causes	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
Purulent pericarditis	2	2.6	75	97.4	0	0.0
Fibrinous pericarditis with effusion	6	20.0	13	43.3	11	36.7
Tuberculous pericarditis	0	0.0	0	0.0	3	100.0
Noninflammatory effusion	2	66.7	0	0.0	1	33.3

## COMMENT AND SUMMARY

One hundred and thirteen cases of pericarditis with effusion in which necropsy was performed at the Mayo Clinic were studied with special reference to correlation of clinical and pathologic data. The cases were grouped according to the character of the effusion as follows: (1) acute purulent pericarditis, (2) fibrinous pericarditis with effusion, (3) tuberculous pericarditis and (4) noninflammatory effusion. A distinct predominance in males occurred. Infections were the etiologic factors in 111 cases (98.2 per cent). Intrathoracic infectious disease occurred with greatest frequency. Infectious processes elsewhere in the body occurred in thirty-one cases (27.4 per cent). Only two cases (1.8 per cent) were found in which infection was absent, both of these cases were examples of primary cardiac disease with congestive failure. From this study, therefore, it appears to be established that the presence of infectious intrathoracic disease offers a great chance of the pericardium being involved, and when infectious processes of the body as a whole are considered, the chance of pericarditis is still greater. Thus, the presence of infections should always focus attention on the pericardium, and the result may be that purulent pericarditis or fibrinous pericarditis with effusion will be recognized more commonly. It is also of interest

to observe the high incidence of pleural effusion occurring with these forms of pericarditis. Fluid was present in one or both pleural cavities in eighty-three cases (73.5 per cent). This observation may be applied as an accessory diagnostic sign that favors the probability of the presence of pericarditis.

The cardiac weights in the sixty cases in which these data were available are presented.

Associated disease of the heart occurred relatively infrequently in these cases of pericarditis with effusion. There were thirty-three cases (29.2 per cent) in which there was associated cardiac disease, which may be compared with 53.5 per cent of cases of adherent pericarditis<sup>4</sup> in which there was such associated disease.

The value of so-called characteristic signs of pericardial effusion is considerable and the presence of any such sign should be properly evaluated, but their absence does not justify failure of recognition of pericarditis with effusion. Complaints predominantly referable to the cardiovascular system occurred in only 13.2 per cent of the cases. The clinical syndrome in the majority of the cases was that of sepsis.

Death resulting directly and solely from heart disease occurred in only 8.8 per cent of the cases, from sepsis, in 77.9 per cent, and from other causes, in 13.3 per cent.

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<sup>4</sup> Smith, H. L., and Williams, F. A. Pericarditis. I. Chronic Adherent Pericarditis, *Arch. Int. Med.*, this issue, p. 171.

# CHOLESTEROL OF THE BLOOD PLASMA IN HEPATIC AND BILIARY DISEASES

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As the liver is involved in a great many activities, it is not at all improbable that dissociated functional disturbances may arise when the organ is injured and that some functions are likely to suffer damage, whereas others remain intact or are only slightly affected. This may account for the invention of so many diverse liver function tests and the failure of any single one to satisfy the need for a uniformly accurate method of determining the functional capacity of the diseased liver. The studies have been directed toward the variations in the normal excretory and metabolic processes with which the liver is concerned. In addition, attempts have been made to evaluate the condition of the organ by increasing the burdens in tolerance tests with sugars, fats and proteins, as well as injection of pigments, exogenous substances such as dyes, cinchophen, etc. A discussion of the value of all these functional probes would be too involved. Summaries and reviews on the subject have been given by Rich,<sup>1</sup> Greene, Snell and Walters,<sup>2</sup> Schondube,<sup>3</sup> Schrumpf,<sup>4</sup> and others, without uniformity in the conclusions. Recently several aspects of the problem have been reported. Shay, Schloss and Rodis<sup>5</sup> revived the Bauer galactose tolerance test as a means of early differentiation of the group of toxic or infectious jaundice. Lichtman and Sobotka<sup>6</sup> evolved a new method of determining tyrosine in the urine by means of the enzyme tyrosinase. Lichtman<sup>7</sup> utilized the ability

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From the Medical Division (Dr. George Baehr) and the Laboratories of Mount Sinai Hospital

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of the liver to oxidize cinchophen, previously ingested, as an index of hepatic function Bernheim<sup>8</sup> employed the intravenous injection of distilled water and the subsequent icterus index values as a liver function test In 1927, von Bergmann<sup>9</sup> introduced the bilirubin tolerance test, injecting the pigment into the blood stream and studying the rate of elimination by the liver as an index of hepatic function Eilbott,<sup>10</sup> his pupil, amplified the work, and recently Harrop and Barron<sup>11</sup> reported its utilization as a test for liver insufficiency

In recent years, considerable attention has been focused on the rôle of the liver in the cholesterol metabolism According to the most recent reviews by workers on the subject—Hueck,<sup>12</sup> Thannhauser,<sup>13</sup> Gardner and Gainsborough,<sup>14</sup> Schonheimer,<sup>15</sup> Burger,<sup>16</sup> etc—the values of the cholesterol in the blood plasma of human beings represent the resultant of many factors It is agreed that the greatest source of the cholesterol in the body is exogenous, and that this alimentary absorption depends on the amount of cholesterol in the ingested food and the presence of fatty acids, bile and pancreatic juices in the intestines There are, however, several endogenous sources which include the destruction of erythrocytes and other body cells, the now accepted synthesis of cholesterol by the organism, and its mobilization from the fat tissue stores and the reticulo-endothelial cells According to Thannhauser, the liver is the main excretory organ of cholesterol and regulates the relative content of the blood in cholesterol and cholesterol ester (the compound of one molecule of cholesterol with one molecule of a fatty acid) One hundred cubic centimeters of normal human plasma contains from 150 to 200 mg of total cholesterol, of which from 50 to 70 per cent is in the form of cholesterol ester

As early as 1862, Austin Flint, Jr,<sup>17</sup> described a new excretory function of the liver which consisted of the removal of cholesterol from the blood, and believed that hypercholesteremia depended on pathologic changes in the liver He also observed hypercholesteremia with obstructive lesions in the biliary tract, a fact noted in more recent years by

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16 Burger, M Ergeb d inn Med u Kinderh **34** 583, 1928

17 Flint, A, Jr Am J M Sc **44** 305, 1862

Chauffard, Laroche and Grigaut,<sup>18</sup> Beumer and Burger,<sup>19</sup> Feigl,<sup>20</sup> Bang,<sup>21</sup> Stepp,<sup>22</sup> Rothschild and Felsen,<sup>23</sup> Chauffard,<sup>24</sup> and others Feigl, using the Bloor method, reported cholesterol values as high as 1,100 mg in 100 cc of blood plasma. Rothschild and Felsen and Stepp noted a direct relationship between the degree of jaundice and cholesteremia in pure, uncomplicated cases of obstructive jaundice. Exceptions to this were noted by Stepp, when factors of cachexia and poor fat resorption supervened over a longer time, and by Rothschild and Felsen, when high temperatures and infection occurred. Furthermore, the latter investigators made an important observation, that in other conditions associated with jaundice—cirrhosis of the liver, acute yellow atrophy, pernicious vomiting of pregnancy—the cholesteremia bore no relation to the intensity of the jaundice. This differentiation, later confirmed by many others, has served an important clinical purpose.

Although Feigl<sup>25</sup> reported low cholesterol ester values in a study of the blood lipoids in acute yellow atrophy, he did not attach any special significance to the observations. Thannhauser and Schaber,<sup>26</sup> later, showed that in cases of damage of the liver the values for cholesterol ester were below those of the free cholesterol, and in the more severe cases (acute yellow atrophy) the esters were much depressed or absent. To this drop in cholesterol esters they attached the name "Estersturz," and attributed the phenomenon to a disturbance in the liver of the synthesis of cholesterol ester from fatty acids and free cholesterol and of the hydrolysis of cholesterol esters into free cholesterol and fatty acids. They consider this reversible reaction dependent on the enzymes of the liver cells, which are disturbed in diffuse parenchymatous lesions. This "Estersturz" was interpreted as indicating liver damage. In disagreement with these authors, Burger and Habs,<sup>27</sup> Stern and Suchantke,<sup>28</sup> and Gardner and Gainsborough<sup>14</sup> did not accept this hypothesis, and considered the drop in ester values to be dependent on the failure of fat

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21 Bang, I. *Biochem Ztschr* **91** 122, 1918

22 Stepp, W. *Beitr z path Anat* **69** 233, 1921

23 Rothschild, M. A., and Felsen, J. The Cholesterol Content of the Blood in Various Hepatic Conditions, *Arch Int Med* **24** 520 (Nov) 1919

24 Chauffard, A. *La lithiase biliaire*, ed 2, Paris, Masson et Cie, 1922

25 Feigl, J. *Biochem Ztschr* **86** 1, 1918

26 Thannhauser, S. J., and Schaber, H. *Klin Wchnschr* **5** 252, 1926

27 Burger, M., and Habs, H. *Klin Wchnschr* **6** 2221, 1927

28 Stern, R., and Suchantke, G. *Arch f exper Path u Pharmakol* **115** 221, 1926

resorption They maintained that the absence of fat resorption from the intestines obliges the body to deesterize the combined cholesterol in the plasma in order to be able to utilize the fatty acid

Adler and Lemmel,<sup>29</sup> in a very extensive study of the blood cholesterol in various hepatic and biliary conditions, agreed with Thannhauser and Schaber that the functions of the liver are intimately related to the regulation of the ratio of total to ester cholesterol in the blood, fat mobilization and movement, excretion and synthesis of cholesterol Through simultaneous investigations of other liver functions, they have concluded that the disturbed cholesterol picture parallels most disturbances in other functions of the liver and reflects parenchymatous liver disease

I<sup>30</sup> found the cholesterol ester values in the blood plasma to be greatly diminished, and even nil, in cases of severe liver disease, and observed them return to normal with improvement in the clinical picture In these cases, bile and urobilin were present in the stools, even when the ester values were very low, so that the theory of disturbed fat and cholesterol resorption as an explanation cannot entirely account for the phenomenon in cases of primary liver diseases My observations support the theory of Thannhauser that the "Estersturz" is the result of diffuse damage to the liver For the past two years, I have also been interested in the blood cholesterol in cases of jaundice of various causes, making repeated observations throughout the entire clinical course from the time of admission to the hospital until the termination of the condition It was hoped that a complete picture might provide a rational understanding of the value of the blood cholesterol partition in the various types of jaundice, and might also explain possible discrepancies

Determinations of the total, free and ester cholesterol content of the blood were carried out on 1 cc of blood plasma taken from the patients in the morning before breakfast Specimens obtained during fasting were utilized because of the work of Gardner,<sup>31</sup> who showed that changes in the cholesterol content of the plasma, as well as in the relation of ester to total cholesterol, occurred during the digestive process Gardner could not explain these changes on an influx of the cholesterol absorbed from the alimentary canal, but considered them as evidence of an active endogenous metabolism during digestion, in which cholesterol takes some part I have employed the method of Bloor and Knudson<sup>32</sup> for my determinations The work was carried out under

29 Adler, A, and Lemmel, H *Deutsches Arch f klin Med* **158** 173, 1928

30 Epstein, E Z The Cholesterol Partition of the Blood Plasma in Parenchymatous Diseases of the Liver, *Arch Int Med* **47** 82 (Jan) 1931

31 Gardner, J A, and Gainsborough, H *Biochem J* **22** 1048, 1928

32 Bloor, W R *J Biol Chem* **24** 227 1916 Bloor, W R, and Knudson, A *ibid* **27** 107, 1916

the constant supervision and with the invaluable aid and suggestions of Dr George Baehr of the Medical Division and of Dr Harry Sobotka of the Chemical Laboratory

#### OBSTRUCTIVE JAUNDICE

Table 1 summarizes the findings in the blood, urine and feces, as well as the operative and necropsy reports in forty-three cases of obstruction to the common bile duct by neoplasms, stones, strictures, carcinomatous glands, etc. In the great majority of instances a pronounced hypercholesteremia was found, which roughly paralleled the amount of blood pigment and the degree of occlusion of the common bile duct. The degree of increase in blood cholesterol varied. The maximum concentration was more than 900 mg per hundred cubic centimeters.

The hypercholesteremia accompanying obstructive jaundice is explained by the work of Eppinger,<sup>33</sup> and Barron and Bumstead,<sup>34</sup> who showed that with impediments to the proper outflow of bile, the bile canaliculi become distended, tortuous and frequently ruptured as a result of the back pressure of the biliary stasis. This results in the outpouring of the bile into the pericapillary lymph spaces and blood stream. Rich, in his exhaustive review,<sup>1</sup> called this the regurgitative type of jaundice. Not only the biliary pigments and acids but concomitantly the cholesterol of the bile are thrown back into the circulation. With the removal of the obstruction, the hypercholesteremia and hyperbilirubinemia lessen and disappear, although the former may persist for a considerable time after the jaundice has cleared up.

This regurgitative hypercholesteremia, which occurred in the majority of cases, was only slight or even lacking in eight instances, although a considerable hyperbilirubinemia was present. The failure of the cholesterol level to parallel the degree of jaundice in all instances was thought to be due to infection, superimposed on the obstruction, cachexia, cholemia and damage to the liver incident to long continued biliary stasis. However, cases 1, 5, 16, 22, 27 and 34 illustrate that hypercholesteremia may occur in spite of cachexia, cholemia, infection and long-standing biliary stasis.

One observes from table 1 that in about half of the cases of obstructive jaundice the ester values rose in proportion to the increase in total cholesterol. In other instances there was an absolute but not a proportionate increase of ester. And in cases 5, 6, 7, 13, 16, 21, 39 and 40, the cholesterol ester was lowered, in spite of the pronounced

33 Eppinger, H. *Beitr z path Anat u z allg Path* **31** 230, 1902

34 Barron, E. S. G., and Bumstead, J. H. *J Exper Med* **47** 999, 1928

TABLE 1—Obstructive Jaundice

Case	Age	Sex	Duration Jaundice Before Admission	Date	Blood						Cholesterol, Mg per 100 Cc			Observations		
					Urine		Stool		Icterus Index	Van den Bergh		Total	Ester		Free per Cent	
					Bile	Urobilin	Bile	Urobilin		Direct	Indirect					
1	60	F	6 wks	2/21	+	0	0	0	125	Pr +	1 15,000	520	175	345	34	Carcinoma of head of pancreas, cachexia
2	52	F	8 wks	2/21	+++	Ft tr	0	+		Pr +	1 14,000	312	70	242	22	Carcinoma of head of pancreas
3	36	F	1 day	7/22	+		Trace	++		Del +	1 65,000	365	219	146	60	Operation stones in common bile and hepatic ducts
4	32	F	1 mo	3/26	+	Trace	0	0	100	Pr +	1 23,000	224	106	118	47	Operation carcinoma of head of pancreas, cholemia, death 4 days postoperatively
5	70	M	4 mos	6/24	+++	+	0	+	200	Pr +	1 7,000	750	50	700	7	Carcinoma of head of pancreas, painless jaundice, enlarged, irregular liver, cachexia
6	32	M	5 wks	7/21 7/28 8/5 8/14	+	++	0	0		Pr +	1 30,000	800	90	710	11	Autopsy adenocarcinoma of rectum, infiltration and occlusion of common bile duct by surrounding metastatic hilus nodes
7	52	M	9 mos	9/3	++	+	0	Ft tr	85	Pr +	1 13,000	536	62	474	11	Autopsy carcinoma of head of pancreas with stenosis of papilla of Vater
8	40	F	4 wks	11/5	++	+	0	0		Pr +	1 15,000	470	268	202	57	Operation carcinoma of head of pancreas with metastases to liver
9	62	F	3 days	11/11	+		Trace			Del +	1 20,000	586	346	240	59	Operation very large stone obstructing common bile duct
10	55	M	7 wks	11/17	++	0	0	0	180	Pr +	1 7,000	340	85	255	25	Carcinoma of head of pancreas with liver metastases and common bile duct obstruction
11	60	M	1 wk	11/10	+++	+				Pr +	1 50,000	536	288	248	54	Operation stone obstructing common bile duct
12	38	M	2 mos remit tent	12/16 12/26 1/3 1/8 1/16 2/3 2/9 2/28	+	++	+	+	55 65 40 30 16 17 30	Pr +	1 25,000	416	190	226	46	Operation obstruction of common bile duct, carcinoma of papilla of Vater, metastases to liver
				++	+	+	Trace		65	Pr +	1 25,000	750	470	280	63	
				Trace	+	+	+		40	Pr +	1 25,000	830	360	470	43	
				0	0	0	0		30	Del +	1 300,000	625	375	250	60	
				0	0	0	0		16			288	225	63	78	
				++	+	+	+		17			280	150	130	53	
				++	+	+	+		30	Pr +	1 25,000	695	375	320	54	
				+			+		75	Pr +	1 25,000	750	375	375	50	

33	53	M	1 mo	1/9 1/13	+++ ++++	Trace 0	Trace Ft tr	140 175	Pr + Pr +	1 8,000 1 8,000	272 310	% Trace	240 ±310	12	Autopsy carcinoma of gallblad- der, metastases to lymph nodes at porta hepatis with infiltra- tion of wall of common bile duct and subsequent stenosis, subacute purulent cholangitis with multiple liver abscesses
14	69	M	10 wks	1/20	++	++		45	Pr +	1 40,000	312	208	104	66	Operation stone removed from common bile duct Cholemia
15	48	F	6 wks	2/5	+++	+++		100	Pr +	1 15,000	214	80	131	37	
15	48	F	6 wks	2/5	+	++		10			535	415	120	77	Carcinoma of rectum (postopera- tive), metastases to porta hepatis
16	64	F	4/30	0	++++	++	++		Pr +	1 50,000	480	40	440	8	Operation large common bile duct stone
17	63	F	2 wks	5/10 5/16	0	+++++		45 36	Pr +	1 50,000	420 416	52 Trace	308 ±416	12	Autopsy purulent cholangitis and cholangietic hepatitis, parenchymatous degeneration of liver
17	63	F	2 wks	5/20 5/26 6/4	+++ ++++	0 0	0 Very ft tr	150	Pr +	1 14,000	750 600 226	234 214 30	516 386 196	31 35 13	Operation carcinoma of papilla of Vater Tube in common bile duct with drainage for 12 days
18	70	F	1 wk	12/11 12/19	+++ +	+++ +	0 +	65 50	Pr + Pr +	1 17,000 1 22,000	312 312	108 190	204 122	34 60	Abdominal malignancy, metas- tases to hilar lymph nodes
19	58	M		12/9 12/26 1/9 1/16	+++ ++ +	+++ ++ ++	Trace	50 40 105	Pr + Pr + Pr +	1 35,000 1 62,000 1 30,000	330 290 156 130	104 80 90	186 76 40	36 51 69	Autopsy common bile duct stone occluding papilla of Vater, obstructive biliary cirrhosis, septic course
20	52	F	5 wks	2/13	++++	+	+	160	Pr +	1 30,000	394	208	186	53	Operation numerous stones in common bile duct
21	44	F	2 days	4/20 5/26 6/6	+	0	0	60 50	Pr +	1 50,000	250 245 170	25 82 45	225 163 125	10 33 26	Operation stone in common bile duct, drainage of common bile duct
22	70	M	6 mos	4/14 4/24	+	+		150 125	Pr +	1 30,000	415 255	75 150	370 105	17 59	Carcinoma of head of pancreas, painless jaundice, weakness, loss of weight, liver large, irregular and nodular, dis- tended gallbladder, cachexia
23	56	M	3 mos	1/8	+++	It tr		120	Pr +	1 17,000	985	625	310	67	Carcinoma of stomach (postop- erative), metastases to liver obstructive jaundice due to metastatic nodes
24	60	M	3 wks	7/1 8/4	++	0	+	50	Pr + Pr +	1 30,000 1 30,000	220 268	80 136	110 132	26 50	Operation large stone in com- mon bile duct

TABLE 1—*Obstructive Jaundice—Continued*

Case	Age	Sex	Duration jaundice Before Admission	Date	Urine			Stool		Icterus Index	Blood		Cholesterol, Mg per 100 Cc			Observations
					Bile	Urobilin		Bile	Urobilin		Direct	Indirect	Total	Ester	Free per Cent	
25	60	M	2 wks	4/11	++++	0		0					625	415	210	66
26	43	M	2 wks	4/ 2	+	0		Very ft tr		42	Pr +	1 50,000	375	90	285	21
27	55	M	3 wks	2/27 3/ 2	+++	+++		+		110	Pr +	1 16,000	680	468	212	66
				3/11	+++	+++		+		60	Del +	1 100,000	935	625	310	67
				3/24	+++	+++				48	Pr +	1 11,000	625	375	250	60
										70			658	428	230	66
28	41	F	10 d	4/10 4/21	+++	Trace				75	Del +	1 50,000	575	235	340	40
					+					45			625	470	155	75
29	43	M	3 wks	1/29 2/ 5 3/ 6	+	0		+	++	35	Del +	1 90,000	355	150	205	42
					Ft tr	+++				25	Neg	1 100,000	536	238	248	54
													340	270	70	79
30	59	M	10 wks	1/20	+	+				45	Pr +	1 40,000	312	208	101	66
				2/ 5	+++	+++				100	Pr +	1 15,000	214	80	134	37
31	73	F	6 wks	5/ 4	Ft tr	Ft tr		+		25	Del +	1 110,000	208	145	63	70
32	62	F	5 wks	1/21	6	0				20			340	95	245	28
33	28	M	6 days	4/23 4/27	++++	0		Trace		140	Pr +	1 14,000	375	170	205	45
					++	0					Del +	1 77,000	416	140	276	34
34	59	M	3 wks	3/13 3/19 4/ 3	+++	0		Trace		200	Pr +	1 6,000	416	234	182	56
					+++					220			350	208	142	59
					+++					250			268	52	216	19
35	54	M	10 wks	5/ 5	++	+		+		80	Pr +	1 43,000	415	180	235	43

36	46	F	3 days	12/26	+		++	15	Del +	1 90,000	312	234	78	71	Cholecystectomy and removal of stone in common bile duct 5 years ago, typical symptomatology of common bile duct obstruction
37	57	F	10 days	1/14 1/29	+		+	56 55	Del + Pr +	1 17,000 1 14,000	315 340	105 104	210 236	33 30	Operation metastatic carcinoma of liver and hilus lymph nodes
38	52	M	5 days	5/11 5/18 5/23 5/26 5/29	++ ++ ++ 0 0	++ ++ ++ 0 0	++ ++ ++ ++ ++	40 50 30 20 37	Del + Del + Del + Del + Pr +	1 33,000 1 36,000 1 100,000 1 170,000 1 65,000	470 326 440 337 278	228 144 208 163 98	242 182 232 194 180	49 44 47 46 35	Incomplete obstruction of common bile duct by stone or neoplasm, fever and chills throughout course
39	69	M	3 days	11/26	+		+++	75	Pr +	1 20,000	234	65	169	28	Common bile duct stone with suppurative cholangitis
				12/ 1	Ft tr	Ft tr	0	25			560	90	170	35	Previous cholecystectomy, recurrent chills, fever and jaundice
				12/26	0		+++	27		1 80,000	250	90	160	36	Biliary fistula, drainage 600 cc purulent bile
				1/ 6	+			15		1 200,000	312	110	202	35	Readmission chills, fever and jaundice, duodenal drainage A and B bile contained pus
				2/28	+			70		1 25,000	125	40	85	32	Readmission chills, fever, severely ill
40	60	M		2/16	+		1 t tr	95	Pr +	1 25,000	156	38	118	24	Autopsy calculi in common bile duct causing occlusion, purulent cholangitis and cholelithic liver abscesses, cholemia
41	38	F		3/17 3/24 3/28	++ ++ +	0 0 0	0 0 0	75 65 80	Del + Pr + Pr +	1 25,000 1 18,000 1 28,000	268 360 380	150 198 150	118 162 230	56 55 39	Operation stricture of common bile duct
42	42	M	4 wks	5/22 6/ 8 6/15	+		+	105 60 30	Pr + Del + Del +	1 30,000 1 100,000 1 100,000	340 312 300	208 110 85	132 202 215	61 35 28	Operation many stones in common bile duct, free biliary drainage
43	72	M	1 wk	6/23	++		+	30	Pr +	1 40,000	312	208	104	67	Obstruction of common bile duct due to carcinoma, aspiration of liver revealed adenocarcinoma cells



hypercholesteremia, so that the relative ratios of total and free to the ester cholesterol were definitely reduced

Burger explained this divergence between ester and free cholesterol as due to a stasis of bile containing a disproportionately large percentage of free cholesterol and a relative diminished ester fraction, also as due to a disturbance of fat metabolism caused by a lack of bile in the intestines. Gardner and Gainsborough offer two theories as an explanation for the reduction of ester in some cases of biliary obstruction. First, with the absence of bile from the intestine, no cholesterol is absorbed from the intestine, and as the normally reabsorbed cholesterol is mainly in the ester form, a reduction in the ester content of the blood results exactly as if the patient were on a sterol-free diet. Secondly, the failure of fat resorption is responsible for a diminution in the available supply of fatty acid for conjugation with cholesterol to form the ester. The absence of fat resorption from the intestines also causes the body to deesterize the preformed cholesterol ester in order to utilize the fatty acid. The ester may therefore be relatively, or even absolutely, reduced in obstructive jaundice when the liver becomes damaged as a result of prolonged biliary stasis, superimposed infection, faulty fat metabolism, cachexia. The relative rôle of each factor is often difficult to evaluate.

Thannhauser and Schaber, and Adler and Lemmel consider the lowered ester as evidence of damage to the liver cells occasioned by the stasis. Eppinger, who first described the effects of increased biliary stasis on the intracellular bile ducts, also showed that with continuation of the stasis, more and more liver cells were disrupted, leading to more or less extensive cell necrosis. Schonheimer<sup>35</sup> showed with isolated loops of intestines, in which no connection with the remaining intestine existed, but with intact circulation, that cholesterol is reabsorbed in spite of the absence of bile. In table 1 will be seen data on cases in which the ester fraction of the blood does not depend on the presence or absence of bile in the intestinal tract or on the duration of the jaundice. Moreover, Gardner and Gainsborough admit cases of hypercholesteremia with high esters in spite of persistent failure of fat resorption.

#### NONOBSTRUCTIVE BILIARY TRACT DISEASE

In the group of cases of nonobstructive biliary tract disease are listed seventeen in which cholecystitis and cholelithiasis were found, without obstruction to the proper outflow of bile. In general, the results, seen in table 2, point to a tendency toward an increased cholesterol content of the blood plasma with normal relationship of the

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<sup>35</sup> Schonheimer, R., and von Behring, H. *Ztschr f physiol Chem* **192**:102, 1930

free to ester fractions This hypercholesteremia can perhaps be considered as expression of a metabolic peculiarity contributing to gall-stone formation, especially as the majority of the cases were in females Rothschild and Wilensky<sup>36</sup> emphasized this relationship in a study of

TABLE 2—*Nonobstructive Biliary Tract Disease*

Case	Age	Sex	Blood			Cholesterol, Mg per 100 Cc				Observations
			Icter us Index	Van den Bergh		Total	Ester	Free	Ester, per Cent	
				Direct	Indirect					
1	66	F				125	60	65	48	Operation chronic chole cystitis, one large stone in gallbladder
2	50	F				268	170	98	63	Roentgenogram of gallblad der showed definite stones
3	42	F				134	65	69	48	Operation numerous stones in gallbladder, none in com mon bile duct
4	34	F		Neg	1 300,000	348	280	68	80	Operation chronic chole cystitis, no calculi found
5	31	F		Neg	1 500,000	234	108	126	46	Operation chronic chole cystitis, stones in gall bladder
6	35	F		Neg	1 500,000	180	125	55	69	Operation chronic and acute cholecystitis, chole lithiasis
7	31	F		Neg	1 500,000	137	106	31	78	Operation chronic and acute cholecystitis, chole lithiasis
8	27	F		Neg	1 500,000	280	110	170	39	Operation chronic chole cystitis and cholelithiasis
9	38	F		Neg	1 500,000	268	150	118	56	Operation chronic chole cystitis, multiple stones in gallbladder and common bile duct
10	32	F	10	Neg	1 300,000	300	154	146	51	Operation stones in gall bladder, none in common bile duct
11	37	F	5	Neg	1 500,000	226	144	82	64	Operation small stones in gallbladder and cystic duct
12	19	F		Neg	1 500,000	228	125	103	55	Operation chronic chole cystitis, stones in gall bladder
13	58	F	35	Neg	1 80,000	175	45	130	26	Operation stones in gall bladder
						162	85	77	52	Two weeks after operation
14	31	M	8	Neg	1 330,000	270	104	166	39	Acute cholecystitis, no oper ation, roentgenogram of gallbladder with dye, no visualization
15	45	F	6	Neg	1 500,000	340	118	222	35	Operation chronic chole cystitis and cholelithiasis
16	42	F	5	Neg	1 500,000	175	88	87	50	Operation chronic chole cystitis and cholelithiasis
17	67	F	6	Neg	1 500,000	300	180	120	60	Cholecystitis, roentgeno gram of gallbladder, no visualization, improved in short time

the blood cholesterol in cholelithiasis However, there are several cases with normal or even low cholesterol figures The latter cannot easily be accounted for, as the usual causes of hypocholesteremia in biliary diseases, such as cachexia, cholemia and superimposed infection, were absent In general, it will be seen that the changes in the cholesterol

36 Rothschild, M A, and Wilensky, A O M Clin North America 3 417, 1919

content of the blood in biliary diseases without obstruction to the outflow of blood are slight and without any particular significance—confirming the previous work of Rothschild and Wilensky,<sup>36</sup> Rothschild and Rosenthal<sup>37</sup> and Campbell<sup>38</sup>

#### JAUNDICE DUE TO PARENCHYMATOUS DISEASES OF THE LIVER

A group of thirty-six cases of jaundice due to diffuse parenchymatous disease of the liver was studied, the parenchymatous degeneration ranged in intensity from the mild degree seen in lobal pneumonia, cardiac decompensation and infections to the severest type occurring in fatal cases of acute yellow atrophy. Included are instances of hepatic degeneration due (1) to medicaments, such as arsphenamine preparations, cinchophen and its derivatives, phenobarbital, and (2) to remote diseases such as pneumonia, infections and cardiac decompensations and (3) to primary liver diseases such as so-called catarrhal jaundice, toxic hepatitis, acute, subacute and chronic yellow atrophy. In general, the cases illustrate the importance of a knowledge of the cholesterol picture of the blood plasma in the primary degenerations of the liver and expand the experiences in this field which were recently published<sup>30</sup>

It will be seen in table 3 that the parallelism between hypercholesteremia and hyperbilirubinemia, seen so commonly in cases of obstructive jaundice, is conspicuously lacking in the cases of severe parenchymatous degeneration of the liver. In the latter the total cholesterol content of the blood plasma is rarely elevated. Usually it is normal or subnormal. In case 20 with a fatal outcome, repeated determinations on 1 cc of plasma gave total figures too low to be estimated. The hypocholesteremia is seen in cases with very marked jaundice, reaching at times an icterus index of 200 and a bilirubinemia of 16,000 by the indirect van den Bergh method. Pronounced reduction in cholesterol affords a means of sharp differentiation between the cases of jaundice due to mechanical obstruction to the outflow of bile and those caused by a primary degenerative lesion of the parenchyma of the liver. This difference, appreciated by Rothschild and Felsen in 1919, has been of service to us in Mount Sinai Hospital as an aid in differential diagnosis. On the contrary, a study of the amount of icterus and the types of bilirubin in the blood has afforded little or no assistance in differential diagnosis. A perusal of tables 1 and 3 will show that the degree of bilirubinemia and types of van den Bergh reactions are similar in the two entirely different conditions, but that in obstructive cases the cholesterol and bilirubin of the blood parallel each other, whereas in the parenchymatous diseases of the liver such an association is lacking. Furthermore, the depression of the total cholesterol in primary hepatic diseases has been used by us

<sup>37</sup> Rothschild, M. A., and Rosenthal, N. *Am J M Sc* **152** 394, 1916

<sup>38</sup> Campbell, J. M. H. *Quart J Med* **18** 123, 1924

as an aid in prognosis. Cases in which a fairly high amount was found at the onset of the disease had a favorable outcome. Cases with a profound depression below the normal usually ended fatally within a short time.

Observations on the cholesterol esters of the blood plasma were even more striking. In cases 3, 5, 11, 14, 18, 19, 20, 26 and 36, the cholesterol esters were very depressed or even absent during the short, stormy course of the disease. The outcome was fatal, and (except case 3 in which no autopsy was obtained) the postmortem examinations revealed severe parenchymatous degeneration of the liver—marked hepatitis, or acute or subacute yellow atrophy.

In cases 1, 2, 7, 9, 10, 17, 31, 34 and 35—with well marked damage of the liver—the initial cholesterol esters were considerably diminished. With improvement in the condition, the esters gradually rose, both relatively and absolutely, until normal values were obtained with the complete recovery. It will be seen that the ester fraction exactly mirrored the degree of severity of the liver damage, consistently remaining very low or absent in the fatal cases and rising gradually to normal in cases showing clinical evidences of improvement.

In the less severe cases of liver damage—6, 8, 12, 23, 24, 28 and 30—the initial cholesterol esters were lowered, but mainly relatively. This moderate lowering of the esters presaged a good prognosis, which was later confirmed by the subsequent improvement in the condition.

Cases 21, 22, 27, 29, 32 and 33 represent instances of jaundice developing in the course of cardiac insufficiency, with chronic passive congestion of the liver, accompanied in several instances by pulmonary infarctions. The development of jaundice in these cases is due to injury to the liver cells during long-standing passive congestion and anoxemia. A moderate lowering of the esters was present in these cases, and the ester level rose to normal again with improvement.

Of particular interest is the fact that in cases 1, 2, 4, 7, 9, 10, 24, 30 and 31, the total cholesterol and ester figures rose above those found in normal blood plasma concomitant with the clinical improvement and the regression of the evidences of damage to the liver. It is conceivable that occasionally a hypercholesteremia in the stage of healing from acute parenchymatous liver degeneration might be confused with a hypercholesteremia of an incomplete biliary obstruction, but the course of events and the clinical picture should offer easy means of differentiation.

The transition from hypocholesteremia to hypercholesteremia with clinical improvement seems to coincide with regression in the degenerative process and with entry into the regenerative stage. The cholesterol picture mirrors the various stages of the pathologic process and reflects the functional capacity of the diseased organ. Two explanations are

TABLE 3—Jaundice Due to Parenchymatous Diseases of the Liver

Case	Age	Sex	Duration Jaundice Before Admission	Date	Urine				Stool		Icterus Index	Blood van den Bergh		Cholesterol, Mg per 100 Cc			Ester, per cent	Observations
					Bile	Urobilin	Bile	Urobilin	Direct	Indirect		Total	Ester	Free				
1	32	M	6 days	4/8 4/14 4/18 4/29	+	+++			+		70 120 75 20	Pr +	1 11,000	150 162 214 300	Trace 57 56 120	150 105 158 180	0 35 26 40	Case of catarrhal jaundice or toxic hepatitis which gradu- ally improved after 5 weeks on a high carbohydrate diet
2	25	M	7 wks	5/14 6/26 6/29 7/6 7/13 7/20	0	+		++		45 35 40 28 30	Del + Del +	1 330,000 1 120,000	144 198 326 356 312	188 40 50 156 0	124 104 118 200 178	60 27 24 43 43	Case of toxic hepatitis, im- proved after 4 weeks	
3	18	F	3 days		+++	+++						Del +	1 300,000	250 277 357 340 135 118	98 90 144 118 138 Trace	132 187 106 239 202 135 118	39 32 57 33 40 0 0	Case of acute yellow atrophy of liver vomiting, bloody and coffee ground in nature, deep ening jaundice, apathy, drowsi- ness, tyrosine in urine, liver percussed small, coma, death in 3 days Toxic hepatitis due to cincho- phen medication
4	47	M	3 days	6/22 6/26 7/9 7/13 7/22	0 ++ ++	++ ++ 0			+	100 55 30 38	Pr + Pr + Del +	1 17,000 1 50,000 1 100,000	250 277 357 340 135 118	98 90 144 118 138 Trace	132 187 106 239 202 135 118	39 32 57 33 40 0 0	Autopsy thrombosis of the branches of the hepatic veins with secondary congestive atrophy of the liver	
5	37	M		2/13 2/29	0 0	++ +		+		60	Neg Neg Pr +	1 500,000 1 300,000 1 26,000	200 202	67 156	133 46	34 77	Acute hepatitis in the course of a lobar pneumonia, jaundice disappeared and patient cured after 5 days	
6	26	M		4/6 4/11	0 0	++ 0			++		120 40	Pr + Del +	1 18,000 1 330,000	120 290 214 268	38 125 106 138	82 165 105 130	32 43 50 52	Arsenic toxic hepatitis, im- proved on high carbohydrate diet
7	20	M	4 days	2/13 2/24 3/6 3/13	++ 0 0 0	++ ++ 0 0			++		35 30	Pr + Pr + Neg	1 19,000 1 40,000 1 500,000	238 250 220	57 70 170	181 180 50	24 28 77	Acute toxic hepatitis following intravenous saline infusions, improved and discharged after 12 weeks
8	52	M	36 hrs	12/16 12/31 2/10	++ ++ ++	++ ++ 0		++		75 35 25 100 100	Pr + Neg Pr + Del + Del +	1 30,000 1 330,000 1 12,000 1 50,000 1 50,000	122 150 276 110 154 312 208 130	0 34 134 0 64 170 125 0	122 116 142 140 90 142 83 130	0 23 19 0 42 54 60 0	Acute toxic hepatitis following phenobarbital ingestion, im- proved gradually Acute toxic hepatitis following cinchophen ingestion, im- proved gradually Autopsy subacute recurrent yel- low atrophy of the liver	
9	40	M		4/2 4/8 4/14	++ ++ ++	++ ++ ++		++				Pr + Neg Pr + Del + Del +	1 30,000 1 330,000 1 12,000 1 50,000 1 50,000	122 150 276 110 154 312 208 130	0 34 134 0 64 170 125 0	122 116 142 140 90 142 83 130	0 23 19 0 42 54 60 0	Acute toxic hepatitis following phenobarbital ingestion, im- proved gradually Acute toxic hepatitis following cinchophen ingestion, im- proved gradually Autopsy subacute recurrent yel- low atrophy of the liver
10	31	F	10 days	5/10 5/17 5/26 6/2	++ ++ ++ ++	++ ++ ++ ++		++				Pr + Neg Pr + Del + Del +	1 30,000 1 330,000 1 12,000 1 50,000 1 50,000	122 150 276 110 154 312 208 130	0 34 134 0 64 170 125 0	122 116 142 140 90 142 83 130	0 23 19 0 42 54 60 0	Acute toxic hepatitis following phenobarbital ingestion, im- proved gradually Acute toxic hepatitis following cinchophen ingestion, im- proved gradually Autopsy subacute recurrent yel- low atrophy of the liver
11	52	F	2 wks	6/24	+	+		+		150	Pr +	1 16,000	130	0	130	0	0	Autopsy subacute recurrent yel- low atrophy of the liver

12	39	F	2 wks	7/12 7/17 7/24	+	++ +++ +	0 0	++ +++ +	0 0	+	++ +++ +	70 30 30	Pr +	1 33,000	135 162 180	50 125 138	85 37 52	37 77 72	Catarrhal jaundice or toxic hepatitis, patent improved after high carbohydrate and low fat diet
13	24	M	2 wks	7/30 8/ 4	+	+	0	+	0	Ft tr ++	200	Pr +	1 7,000	134 188	Trace 60	Trace 128	0 32	0	Catarrhal jaundice, went home 11 days after admission against advice
14	37	F	3 wks	10/16 10/27	++ ++	++ +		++ +			140	Pr +	1 8,000 1 50,000	173 104 100	65 0 36	108 104 64	38 0 36	0	Autopsy acute yellow atrophy of the liver and marked jaundice
15	41	M																	Autopsy lobar pneumonia with parenchymatous degeneration of the liver and marked jaundice
16	38	M	4 days	1/ 5	+	+		+			50			200	50	150	25		Lobar pneumonia involving both lungs, cirrhosis of liver, splenomegaly, hepatitis at autopsy
17	26	M	16 days	1/15 1/17 2/ 3	+	0 ++ +		0 ++ +			75	Pr +	1 40,000	146 108 228	Trace Trace 98	Trace 108 130	0 0 42	0	Acute toxic hepatitis due to arsphenamine injections
18	59	M	1 wk	1/15 1/19	+	0 0	+	0 0	+	+	55	Pr +	1 60,000	100 50	0 0	100 50	0 0	0	Autopsy acute yellow atrophy of the liver
19	26	M	3 wks	5/23 5/26	++ ++	++ ++		++ ++		+	200	Pr +	1 7,000	140 102	Trace 0	Trace 140 120	0 0 0	0	Autopsy subacute yellow atrophy of liver with areas of regeneration
20	12	F	2 mos	4/13 4/17 4/23	++ ++ ++	++ ++ +		++ ++ Trace			120 160 120	Pr + Pr + Pr +	1 20,000 1 14,000 1 14,000	58 70 65	0 0 0	58 70 65	0 0 0	0	Autopsy subacute yellow atrophy of liver with coarse nodular cirrhosis
21	42	M	3 wks	5/19 5/26 4/14 4/20	++ ++ 0 0	++ ++ ++ Trace		++ ++ ++ Trace		+++ +++ ++	120 160 110 120 22 15	Neg	1 170,000	211 250	60 134	154 116	28 54		Rheumatic cardiovascular disease with decompensation and jaundice, improved with rest in bed and digitalis
22	73	F		5/ 5							17			192	50	142	26		Autopsy chronic valvular disease of mitral and aortic valves, hemorrhagic infarct in right lower lobe, chronic passive congestion of liver
23	24	M	2 wks	9/ 8	+++	+++		+++		+++	60	Del +	1 22,000	180	40	140	22		Acute toxic hepatitis or catarrhal jaundice, improved in a month
24	29	M	1 wks	10/30 11/ 6 11/13	0 0 0	++ 0 +	+	++ ++ ++	+		12 15 160	Ft tr Dir +	1 100,000 1 10,000	234 208 328 140	70 134 102 Trace	164 74 226 140	30 62 30 40		Syphilis, arsphenamine toxic hepatitis, improved
25	29	M	6 days		++ ++	++ ++	+	++ ++	+	+		Pr +	1 12,000	80	0	80	0		Toxic hepatitis after neocarphenamine
26	48	F	6 wks		++	+		+		0				80	0	80	0		Autopsy chronic hepatitis and cholangitis with jaundice, hyperplastic thyroid
27	63	M	2 mos		++ ++	++ ++	+	++ ++	+	+	120	Pr +	1 12,000	140	30	110	21		Autopsy mitral and aortic stenosis and insufficiency, pulmonary infarction, chronic passive liver congestion, jaundice

TABLE 3—Jaundice Due to Parenchymatous Diseases of the Liver—Continued

Case	Age	Sex	Duration Jaundice Before Admission	Urine			Stool		Icterus Index	Blood		Cholesterol, Mg per 100 Cc			Observations	
				Bile	Urobilin	Date	Bile	Urobilin		Direct	Indirect	Total	Ester	Free per Cent		
28	21	M	1 day	+++	++		+	++	60	Pr +	1 100,000	150	30	120	20	Syphilitic hepatitis, secondary syphilis, after bismuth intra muscularly and mercury inunctions jaundice gradually disappeared
29	38	F		+++	++			++	22	Del +	1 140,000	120	30	90	25	Rheumatic cardiac disease with congestive failure, pulmonary infarcts, ascites, enlarged liver, improved
30	45	F	1 day	0	++	3/17		++	50	Pr +	1 28,000	180	80	100	44	Arsphenamine toxic hepatitis, improved in short time
31	25	M	10 days	Trace	++	3/21		++	30	Del +	1 140,000	208	98	110	47	Following medication, jaundice developed with dark urine and clay stools liver not palpated, percussed fourth right inter space to costal margin in nipple line
				Trace	++	3/24		++	120	Pr +	1 12,000	278	125	153	45	
				++++	0	5/12	0	+	+			231	0	234	0	
				++++	++	5/18	0	+				223	84	139	37	
				++++	+	5/19	0	+				174	46	128	26	
32	21	M		+++	++	5/26	0	+	36		1 60 000	208	40	168	19	Seriously ill with bad hemorrhagic throat infection
33	32	M	4/ 4 4/18	+++	++	5/29	Trace	Very ft tr	210	Pr +	1 6,000	195	45	130	23	Liver became palpable 1 finger breadth below costal margin patient greatly improved
				++	++	6/ 6		+	180	Pr +	1 11,000	288	163	125	56	
				++	+	6/15		+			340	170	170	50		
34	43	M		++	++						1 60 000	156	Trace	±156	±0	Rheumatic cardiovascular disease with decompensation and jaundice, pulmonary infarction
35	46	M	5 wks	0	++	4/ 4 4/18			13	Neg	1 500,000	220	50	170	23	Triosteal, rheumatic cardiovascular disease with decompensation, jaundice, liver down to umbilicus, hard, pulsating, tender, rest in bed brought rapid improvement
				+	+	6/ 6					220	110	110	50		
						6/30		0								
36	16	F	1 mo	+	Very ft tr	6/12		++			1 500,000	116	Trace	±116	±0	Following injection of arsphenamine fever, vomiting, red urine and diffuse dermatitis developed, no jaundice acutely ill, liver and spleen palpable, improved on high carbohydrate diet, hepatitis (?) without jaundice
				+	+	6/17		+			1 12,000	220	47	173	21	Five weeks ago jaundice followed by ascites, repeated paracenteses in hospital
				0	++	6/30		0				200	118	82	59	Tyrosine in urine
				++	++	10/ 9		++			1 60 000	60	Trace	60	0	Toxic jaundice with coarse nodular cirrhosis, improved but ascites continued to recur
				+	+	10/11		+			1 200,000	174	125	49	72	Autopsy, subacute yellow atrophy, coarse nodular cirrhosis of liver
				+	+	11/ 6		+								
				+	+	6/11		+			1 50,000	150	56	94	37	
				+	+	7/ 6		+				108	Trace	±108	0	

TABLE 4—*Atrophic Cirrhosis of the Liver*

Case	Age	Sex	Urine			Stool		Icterus Index	Blood		Cholesterol, Mg per 100 Cc			Observations	
			Bile	Urobilin		Bile	Urobilin		Direct	van den Bergh	Total	Ester	Free per Cent		Ester, per Cent
1	39	M	0	+				10	Neg	1 500,000	190 160	100 108	90 52	53 68	Chronic alcoholism for many years, ascites, hematemesis and melena present three months ago on first admission
2	61	F						8			208	140	68	67	Repeated alcoholic sprees for past five years, enlarged, hard, irregular liver, spleen not palpable
3	64	M	0	+							156	117	39	75	Autopsy atrophic portal cirrhosis with adenoma
4	40	F	Trace Trace	++ +				25	Del +	1 100,000	195 210	94 114	101 96	48 54	Long history of alcoholism, jaundice developed following alcoholic spree 6 weeks before admission, liver enlarged, spleen palpable
5	66	F						11	Neg	1 500,000	208	106	102	51	Autopsy atrophic cirrhosis of liver ascites, splenic enlargement, ruptured esophageal varices
6	48	M	0	+++	+	+		45			122	46	73	38	Prominent veins of abdominal wall, ascites, large spleen, subicteric, beginning of impairment of liver function
7	45	M	0 0	++ +				12 10	Del + Neg	1 500 000 1 500,000	270 268	60 108	190 160	24 40	Patient entered with ascites, subicterus, dye, galactose, etc, showed hepatic parenchymatous degeneration in Laenec's cirrhosis, patient improved, no ascites, evidences of collateral cutaneous circulation
8	33	M	0	++		+		7	Neg	1 500,000	132	70	62	53	Attacks of diarrhea and epistaxis liver enlarged 2 fingerbreadths below costal margin edge thin, irregular, spleen markedly enlarged
9	47	M						5	Neg	1 500,000	144	90	54	62	Heavy imbibition of whiskey 25 years, liver irregular, tender, 3 fingerbreadths below costal margin, tarry stools, no ascites
10	63	F						16	Neg	1 100,000	150	84	66	56	Autopsy atrophic cirrhosis of liver with multiple adenoma



offered for the occurrence of a hypercholesteremia in the stage of improvement, viz (1) as the regenerative islands of liver tissue have their bile ducts shut off from the rest of the biliary system, an obstructive jaundice occurs with resulting hypercholesteremia, or (2) as the liver functions improve, it is conceivable that only partial functional recovery might occur, with the cholesterol excretion lagging behind the others

#### ATROPHIC CIRRHOSIS OF THE LIVER (LAENNEC TYPE)

Ten cases of atrophic cirrhosis of the liver were studied. The process in this type of hepatic disease is slow and drawn out in its evolution, in sharp contrast to the acute parenchymatous diseases of the liver. It will be seen in table 4 that in cases 1, 2, 3, 4, 5, 8, 9 and 10 the values for total cholesterol and ester in the plasma lie within the normal limits. In cases 6 and 7, in which evidences of superimposed liver damage were present, the ester values were subnormal, and in case 7, it rose again as the condition of the patient improved. This normal cholesterol blood picture is in agreement with the work of Adler and Lemmel, who observed deviations in the cholesterol level only when a superimposed hepatitis or state of coma developed in a patient with Laennec's cirrhosis. Low figures for cholesterol and cholesterol ester are as a rule only seen in the terminal stage of the disease.

#### COMMENT

A study of the blood cholesterol in various forms of hepatic and biliary disease has yielded instructive and important data, which are of assistance in the differentiation between certain types of jaundice and in the prognosis of the various primary liver degenerations.

In forty-three cases of obstruction of the common bile duct by neoplasms, stones, stricture, carcinomatous glands, a hypercholesteremia was usually present which paralleled the bilirubinemia and the degree of obstruction. The hypercholesteremia and hyperbilirubinemia disappear with the removal of the impediment to the biliary outflow, although the hypercholesteremia may persist for a considerable time after the jaundice has cleared up. Both the hypercholesteremia and the hyperbilirubinemia in obstructive jaundice represent a pure regurgitation phenomenon due to the rupture of the bile canaliculi into the lymph and blood channels. In severe cachexia, long-standing jaundice with cholemia, and in infections superimposed in the biliary tract system, the hypercholesteremia often fails to reach levels proportionate to the hyperbilirubinemia, and it may even be absent.

In about one half of the cases, the cholesterol esters rose proportionately with the free cholesterol. In other cases, the ester fraction, although absolutely increased, did not rise sufficiently to maintain the

normal ratio In eight cases among the forty-three, there was a definite fall of cholesterol ester This dissociation between total and ester cholesterol probably depends on several factors Burger and Habs, and Gardner and Gainsborough ascribed it to a one-sided increase of free cholesterol as a result of stasis of bile cholesterol, which is always free cholesterol, and to faulty fat metabolism incident to absence of bile from the intestines Thannhauser and Schabel, and Adler and Lemmel considered the ester fall as an expression of liver damage induced by prolonged biliary stasis, superimposed infections and cachexia That no one factor can explain the phenomenon is illustrated by cases described by Gainsborough and Gardner, as well as by us, in which high cholesterol esters existed in the blood plasma, in spite of prolonged biliary obstruction and faulty fat absorption

Thirty-six cases of jaundice due to parenchymatous diseases of the liver were studied In the more severe hepatic degenerations, the total cholesterol content of the blood plasma was below normal, and in the fatal cases, considerably subnormal Pronounced lowering of the total cholesterol occurred in the gravest cases—a practically normal level in the less severe cases of parenchymatous liver diseases, in spite of a concomitant marked hyperbilirubinemia This offers a sharp means of differentiation from jaundice due to obstruction of the common bile duct, in which the hypercholesteremia closely parallels the degree of hyperbilirubinemia In other words, the hyperbilirubinemia and hypercholesteremia are parallel in obstructive jaundice and dissociated in the primary degenerations of the liver When the dissociation has been very marked, low total cholesterol values with intense jaundice, the outcome has usually been unfavorable

The cholesterol ester changes are even more striking The drop in esters has more or less paralleled the severity of the damage to the parenchyma of the liver In the very acute and severe cases of hepatic degeneration with fatal outcome, the esters were absent at the onset and throughout the duration of the disease In the moderately severe cases, the esters were considerably lowered, but rose gradually to normal with improvement in the condition The ester determinations have therefore proved to be not only of diagnostic import in the recognition of parenchymatous damage, but of extreme value in the prognosis of the disease

In the stage of recovery from liver damage, the figures sometimes rise above normal both for ester and total cholesterol This change from hypocholesteremia to hypercholesteremia is construed as evidence of transition from predominately destructive to regenerative changes The hypercholesteremia of regeneration may last for a considerable time

In seventeen cases of cholecystitis and cholelithiasis with no jaundice and no obstruction of the common bile duct, the total, free and ester cholesterol did not vary significantly from normal, except perhaps for a tendency to a high normal or even slight hypercholesteremia in a few instances

Ten cases of atrophic cirrhosis of the liver (Laennec type) were studied. The values for cholesterol, both total and ester, were within the normal range, except when an intercurrent hepatitis or liver degeneration was superimposed in the terminal stage of the disease

#### SUMMARY

1 Improvement in the accuracy of diagnosis and prognosis of various hepatic and biliary diseases is possible by means of a quantitative study of the blood cholesterol and cholesterol ester—a simple method requiring only 1 cc of blood plasma and allowing repeated determinations throughout the course of the ailment

2 In obstructive jaundice, hypercholesteremia is usually encountered. It roughly parallels the degree of obstruction and the bilirubinemia and returns to normal with relief of the obstruction. Exceptions are noted in cases of marked cachexia, cholemia and superimposed infections. The cholesterol esters in mechanical obstruction rise concomitantly with the total cholesterol in about half the cases, in the other instances they remain normal but lag relatively behind the increased free cholesterol

3 In degenerative diseases of the liver, a pronounced divergence between the bilirubinemia and cholesteremia usually occurs, the more severe the damage to the liver, the greater the tendency to hypocholesteremia. This divergence between the hyperbilirubinemia and the cholesteremia offers a means of differentiation from the cases of mechanical obstruction. In parenchymatous degeneration of the liver, a drop in cholesterol esters parallels the severity of the damage even more accurately. In the rapidly fatal cases the cholesterol esters are very low or absent throughout the course of the disease, in less severe cases, the initial low ester values eventually rise with improvement in the condition

4 In atrophic cirrhosis of the liver (Laennec), the cholesterol blood pictures remain normal. Variations occur only when hepatitis or degeneration of the liver are superimposed in the terminal stage of the disease

5 In cholecystitis and cholelithiasis with no obstruction to the biliary outflow, the blood cholesterol figures are normal or insignificantly elevated

# ANEMIA ASSOCIATED WITH BILIARY FISTULA

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Confronted with a case of severe anemia in an elderly woman, in which there had been a discharge of large quantities of bile through an external fistula more or less continuously for about three years, I naturally thought that it was a terminal condition due to malignancy, especially as the diagnosis of cancer had been made at the time of operative drainage. The question of pernicious anemia arose, however, on account of the complete achlorhydria and the progressive weakness of the patient over a period of several weeks. Liver extract no 343 and preparations of fresh liver were therefore administered, with apparently no response, in fact, the cell count dropped from 1,360,000 red cells and 4,600 white cells on the patient's admission to the hospital to 1,050,000 red cells and 3,700 white cells twelve days later. Ferrous arsenite had also been given intramuscularly during this period. The total failure of these methods of treatment seemed definitely to confirm the diagnosis of secondary anemia due to cancer of the gallbladder.

An enormous flow of bile from an emaciated patient probably suggested therapy with bile salts on the general principle of a deficiency syndrome. It was somewhat of a surprise when it was found that from the date that the bile salts were added to the previous therapy, the red cells and hemoglobin began steadily to rise, and that the reticulocytes, which under liver therapy alone showed no signs of change, began to show a moderate increase in number. The red cells, which on admission showed marked changes in shape and size, also began to resume their normal contour.

A search through the medical literature revealed surprisingly little exact information on this subject. Pfaff and Balch, of the Harvard Medical School<sup>1</sup> had made careful observations on a woman with a biliary fistula. After the administration of pills of human bile and then pills of ox bile, the patient's weight increased 14 pounds (6,400 Gm), and she was in excellent health during the ninety-seven day period of observation. Without exception, textbooks on surgery, including those of an earlier period when external biliary fistula was more frequent, and those published up to the present, dismiss the subject of the loss of bile as a matter of little importance to the human organism. This

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1 Pfaff and Balch J Exper Med 2 49, 1897

literature was carefully reviewed by Wangensteen,<sup>2</sup> and he concluded by saying, "I have failed to find any reference to injurious effect from prolonged loss of bile to the exterior" In the literature, I found only several vague references to anemia as a sequence to the continued loss of bile

In contradistinction to this paucity of careful observation in the human being, within the past ten years, physiologists have published a voluminous literature on the results of a series of observations on external biliary fistula in dogs This experimental work on dogs seems to show that prolonged loss of bile through an external fistula produces a definite anemia which is not due to a digestive disturbance but to a loss of some element discharged with the bile In comparing the clinical case reported in this paper with these experimental anemias in dogs, one could not but be struck with the marked similarity between the two as to cause, symptoms and the results of treatment

Seyderhelm and Tammann<sup>3</sup> and also Baumann<sup>4</sup> concluded that the anemia found in dogs with external biliary fistula, while temporarily relieved by the feeding of bile salts, was bound up with the vitamin D factor in the circulation

From their observations on bile fistulas, Whipple and Smith<sup>5</sup> believe that there is a disturbed physiologic condition related to the lack of the normal internal circulation of the bile salts, that bile salts give a strong stimulation to the liver cells, and that this fact has an important relation to the formation of hemoglobin

#### REPORT OF CASE

Mrs M F, aged 73, was admitted to the Evanston Hospital on July 6, 1930, showing marked prostration, emaciation, flabby parchment-like, ivory-tinted skin, a blood pressure of 88 systolic and 40 diastolic, weakness and apathy On admission the blood count showed 24 per cent hemoglobin, 1,360,000 red cells and 4,600 white cells Some of the red cells had markedly pale-stained central areas, there were anisocytoses and poikilocytoses, marked slight polychromatophilia, no nucleated red cells and some stippled red cells

The patient had been seen in her home in June, 1927, with what appeared to be an obstruction in the biliary system, with nausea, jaundice, etc The illness was prolonged over several weeks In a patient, 70 years of age, there was a presumption of malignant condition During a later attack in August of the same year, the gallbladder was drained at another hospital, and the postoperative diagnosis was cancer of that organ During the winter of 1928, there had been short periods when the fistulous tract closed, but there had been more or less continuous leakage

<sup>2</sup> Wangensteen, Owen H Complete External Biliary Fistula, *J A M A* **93** 1199 (Oct 19) 1929

<sup>3</sup> Seyderhelm and Tammann *Ztschr f d ges exper Med* **68** 539, 1929

<sup>4</sup> Baumann, W *Ztschr f d ges exper Med* **75** 401, 1931

<sup>5</sup> Whipple, G H, and Smith, H P *J Biol Chem* **89** 727 (Sept 30) 1930

ever since. Examination of the stools sometimes showed traces of bile, but usually it gave negative results. The present attack began with dyspnea on exertion and general weakness, which had been progressive and had extended over several weeks. Urinalysis showed albumin, 1 plus, and bile, negative, contents of the stomach showed no free hydrochloric acid. The reticulocytes were recorded as 2 in 500 cells. The blood count on July 19 revealed hemoglobin, 25 per cent, red cells, 1,050,000 and white cells, 3,200 and on August 29 hemoglobin, 68 per cent, red cells, 3,200,000 and white cells, 7,750. The red cells gradually resumed their normal appearance, and the number of reticulocytes increased to 6 per five hundred cells.

Therapy with iron and arsenic was begun on admission, liver therapy was begun on the fourth day. Bile therapy was begun on July 19. After the patient left the hospital, liver therapy was discontinued, and the administration of bile salts was continued, with the addition alternately of iron and arsenic and cod liver oil. The blood picture became entirely normal and continued so. During the summer of 1931, the patient was given bile salts and glutamic acid only, and after a number of weeks during which neither iron nor cod liver oil was given, the blood count showed 100 per cent hemoglobin, 4,990,000 red cells and 10,400 white cells. Recently, however, it was found necessary to give iron and arsenic.

#### SUMMARY

After losing bile through an external biliary fistula for three years, an elderly woman presenting symptoms of severe anemia, prostration and achlorhydria, simulating pernicious anemia but not influenced by liver therapy, immediately began to improve on addition of bile salts. At the time of writing, eighteen months after the attack, she is in excellent health. Bile salts and some form of acid therapy have been given for the achlorhydria; other methods of therapy have been employed from time to time, only bile salts and hydrochloric acid being given at times.

The patient has continued to be in good health, the blood has been in an average, normal condition up to the time of writing, and bile salts and hydrochloric or glutamic acid have been given as the only constant therapy.

It is deemed correct to call this case one of secondary anemia due to the continued loss of bile through an external biliary fistula.

# CARBOHYDRATE METABOLISM IN A CASE OF HEMOCHROMATOSIS

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AND

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The progressively increasing severity of the diabetes that occurs with hemochromatosis has been recognized since the earliest description of that disease sixty years ago. The symptoms of diabetes have been the complaints that have forced the majority of patients with hemochromatosis to seek medical advice, and before the advent of insulin, diabetic acidosis was the most frequent cause of death in these patients. Since the use of insulin, the peculiarities of the responses to insulin therapy have been repeatedly noted.

In a previous article<sup>1</sup> were reported the clinical and pathologic findings in two cases of hemochromatosis with extensive purpura resembling that of scurvy. One of these (case 2 of the previous report<sup>1</sup>) was observed in the hospital for three hundred and seventy-one days. It is the purpose in this article to present and discuss the course of the diabetes in this case.

## REPORT OF CASE

A widowed, white, American man, a truck driver, 42 years of age, was admitted to the medical service on May 23, 1928, with a history of swollen, bleeding gums for five months, progressive weakness, pains in the joints and muscles and spreading purpura for six weeks preceding entrance. For at least six months his diet had been wholly lacking in fruit and green vegetables and had been inadequate in all respects. His weight on admission was 123 pounds (55.8 Kg), there had been a loss of 32 pounds (14.5 Kg) during the preceding year. There had been no symptoms directly referable to diabetes. At the time of admission, the urine was normal, except for the slightest possible trace of albumin and a trace of urobilin.

In view of the possibility of scurvy suggested by the clinical picture, the patient was given large quantities of orange and lemon juice within twenty-four hours and was subsequently given an antiscorbutic diet liberal in carbohydrates. On such a diet his improvement was rapid.

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1 Stetson, R. P., and Ferris, H. W. Hemochromatosis and Purpura, Arch Int Med, this issue, p. 232.

Glycosuria during the first month of hospitalization was rare and of slight degree. At the end of this period it had definitely increased, and the venous blood sugar during fasting was 139 mg per hundred cubic centimeters. The patient was given a measured diet consisting of carbohydrate, 150 Gm, protein, 70 Gm, fat, 225 Gm and calories, 2,900. This abolished the glycosuria, but did not produce a satisfactory gain in weight. The protein and fat were then increased to yield 3,600 calories (table 1, period I). It became necessary to give insulin for the first time ten weeks after admission. Periods II and III demonstrate a progressive impairment of carbohydrate metabolism as measured by increasing glycosuria in spite of rising doses of insulin.

In October (period III), after exhibiting a steady decrease in carbohydrate tolerance for three months, the patient experienced a series of hypoglycemic reactions, occurring usually about midnight. In spite of this, he developed a marked over-night rise in blood sugar concentration, with glycosuria and often slight ketonuria. A division of his evening feeding and insulin between supper and 10 p. m. served to abort the hypoglycemic reactions for a time, but was only moderately successful in clearing the over-night glycosuria.

During the next four months (periods IV and V) the carbohydrate tolerance apparently improved. The development of circulatory failure with auricular fibrillation during the last month of observation (period VI) made it difficult to evaluate the diabetic condition during that period. The patient died in coma on May 28, 1929. The concentration of the venous blood sugar three hours before death was 340 mg per hundred cubic centimeters. The patient did not have diabetic acidosis at the time of death, but presented the terminal picture of hepatic disease.

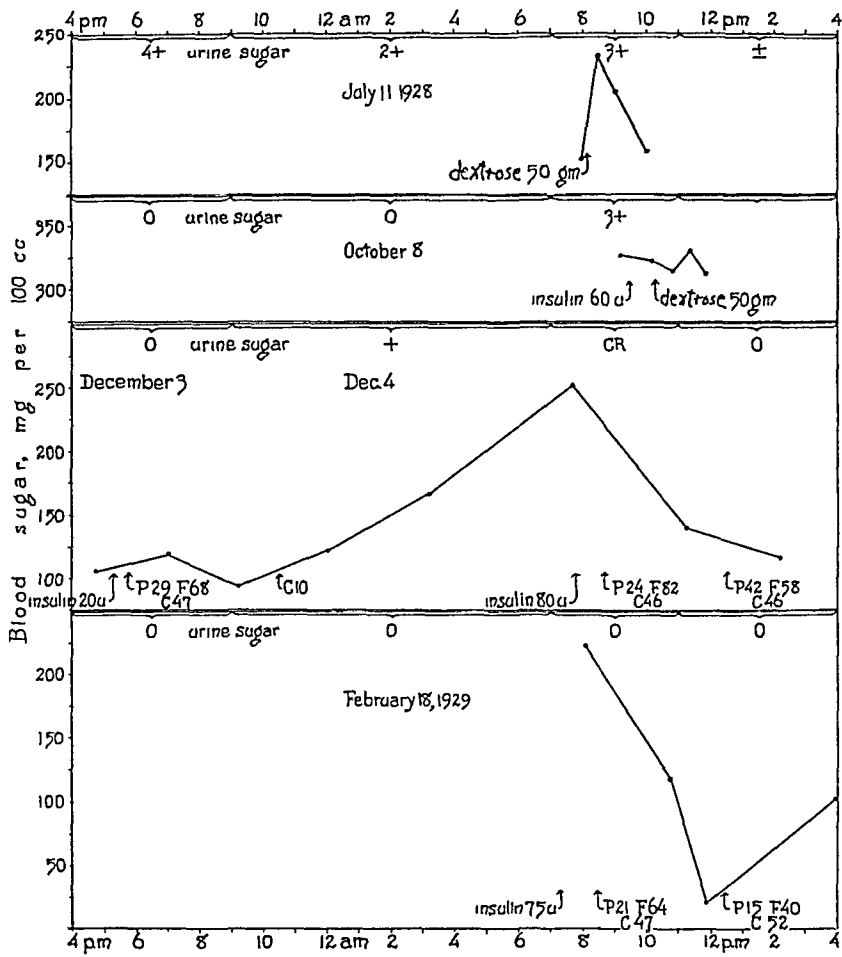
#### COMMENT

In the chart are shown blood sugar curves secured at various stages of the disease. Although the four curves are not comparable in all respects, all show the reaction to about 50 Gm of carbohydrate in the post alimentary period. The first study, made in the early stages of the diabetes when insulin was not required to control glycosuria, represents the hyperglycemic reaction to 50 Gm of dextrose without insulin. The second, taken later in the disease, represents the reaction to 50 Gm of dextrose and 60 units of insulin. The third curve, still later, shows the reaction to the regular breakfast, containing about 50 Gm of carbohydrate, with 80 units of insulin. The fourth curve shows the course of the blood sugar throughout twenty-four hours when the disease was still further advanced,<sup>1</sup> but includes a period comparable to that of the third study.

Between the first and second studies there was a striking increase in the blood sugar concentration during fasting and a diminution of carbohydrate tolerance, evidencing itself in the fact that the second blood sugar curve is far higher than the first, despite the administration of insulin. At the time of the second curve the patient was receiving 60 units of insulin before breakfast and 50 units before supper. In spite of the large evening dose, the blood sugar rose during the night to reach an extremely high level before breakfast. That this rise occurred only during the later hours of the night is indicated by the



facts that sugar did not appear in the urine until after 7 a m , and that there was a severe reaction to insulin at 2 a m of the night following the study of the blood sugar (October 9) The third curve illustrates clearly the over-night rise in blood sugar By this time it had become necessary to alter the dosage of insulin to 80 units one hour before breakfast and 20 units thirty minutes before supper and to administer 10 Gm of carbohydrate at 10 30 p m to prevent insulin



Cutaneous blood sugar curves at various stages of the disease The urine sugar was determined by Benedict's qualitative method in specimens of urine divided into four fractions, collected at 7 a m , 11 a m , 4 p m and 9 p m The results of these analyses are shown above each curve CR indicates complete reduction of Benedict's solution, +, 2+, 3+ and 4+, various degrees of partial reduction The administration of insulin and food is represented by the arrows The nature and quantity of food are represented by the letters, P = protein, F = fat and C = carbohydrate, followed by figures indicating the number of grams of each food given

shock from occurring during the night The large morning dose usually enabled the patient to avoid both glycosuria and shock during the day while he was receiving carbohydrate at intervals At night

a relatively small dose without carbohydrate precipitated shock, although it did not prevent a subsequent rise of blood sugar to a level that initiated glycosuria. As shown in the last curve made, although the blood sugar started at about the same level, a smaller dose of insulin, 75 units, caused a more precipitate fall of blood sugar, ending in shock before lunch. By this time, however, it had become necessary to divide the insulin into three doses: 75 units before breakfast, 10 units before supper and 25 units with 10 Gm of carbohydrate at midnight. The amount of both the protein and the carbohydrate of the diet were kept practically unchanged throughout the course of the disease, the amount of fat was varied slightly.

*The Diabetic Course During the Last Ten Months of Observation*

Period, 1928	Diet			Wt , Lbs	Urine*				Blood Sugar, Insulin, Fasting Daily Venous, Aver		Reactions	
	Pro tein, Gm	Fat, Gm	Car bohy- drate, Gm		7 a m to 9 p m		9 p m to 7 a m		Mg per 100 Cc	age Units	No in Period	Usual time
					Sugar	Ace tone	Sugar	Ace tone				
I July Sept	80	300	150	125 134	0 4+	0	0	0	150	0-30	0	
II Sept Oct	80	300	150	134 140	0 2+	0	0 1+	0	260	95	3	Mid night
III Oct Nov	80	300	150	140 143	1+ 3+	0 2+	4+ 0	0 1+	327	120	5	2 a m
IV Dec Mar	80	200	150	140 143	0 4+	0 1+	0 3+	0 1+	250	100	10	Noon
V April, 1929	80	200	135	142 148	0 3+	0 1+	0 4+	0 1+		70	1	5 p m
VI May	60	170	130	148 171	0	0	0	0	116	52	3	Irreg ular

\* The urine sugar was determined by Benedict's test, urine acetone was determined by the nitroprusside test

The spectacular rapidity with which carbohydrate tolerance deteriorated is shown in the table. The tendency for the blood sugar to rise in the latter part of the night is a well recognized characteristic of severe diabetes and does not distinguish this patient from others without hemochromatosis. The line between glycosuria and shock was, however, peculiarly fine. At times a reaction would occur without a change in diet or insulin, again, an increase of 5 units would precipitate a reaction when there had been profuse glycosuria with the lower dosage. The reactions were sudden in onset, became progressively more severe and were increasingly often associated with paroxysmal auricular fibrillation. Especially in the latter weeks, orange juice given by mouth was not always sufficient to forestall an oncoming reaction. Dextrose given intravenously was always rapidly effective. Other

observers<sup>2</sup> have noted similar fluctuations in carbohydrate tolerance as well as peculiar hypoglycemic reactions in patients with hemochromatosis under insulin therapy

Callender<sup>2c</sup> has suggested that the loss of available carbohydrate reserve that results from the depletion of hepatic glycogen in advanced disease of the liver is of major importance in the production of the hypoglycemic reactions following the administration of insulin in hemochromatosis. Glycogenesis in the liver is one of the means of disposing of ingested carbohydrate, and the hepatic glycogen thus formed becomes the chief source from which carbohydrate can be rapidly mobilized when needed. Mann and his associates<sup>3</sup> showed that in a dog deprived of both liver and pancreas, greater hyperglycemia develops after the administration of dextrose than in a depancreatized animal, and, at the same time hypoglycemic symptoms develop more rapidly and at higher blood sugar concentrations than in a hepatectomized animal. In hemochromatosis simultaneous advance of the disease in the liver and pancreas should bring about a comparable state.

That the ability to form and store glycogen in the liver was never completely abolished in this patient is suggested by the nocturnal rises in blood sugar in the last three curves in the chart. Even in the last few hours of life the blood sugar remained continuously above 300 mg per hundred cubic centimeters. It is, however, probable that the glycogen capacity of the liver was unusually small. This would reduce the immediate effectiveness of insulin in disposing of a given dose of carbohydrate, by compelling the organism to rely more completely on the processes of oxidation for its removal, and, at the same time would afford a smaller amount of rapidly available reserve carbohydrate for emergency needs. Nevertheless, when insulin is not acting, continuous,

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2 (a) Allan, F. N., and Constam, G. R. Insulin Resistance in a Case of Bronze Diabetes, *M. Clin. North America* **12** 1677, 1929. (b) Althausen, T. S., and Kerr, W. J. Hemochromatosis. A Report of Three Cases with Results of Insulin Therapy in One Case, *Endocrinology* **11** 377, 1927. (c) Callender, G. R. Hemochromatosis, *Internat. Clin.* **2** 268, 1928. (d) Eusterman, G. B. Hemochromatosis, Case Report, *M. Clin. North America* **11** 1376, 1928. (e) Hernandez, I. M., and Benaros, M. Case of Bronze Diabetes, *Rev. Soc. de med. int. y Soc. de fisiol.* **6** 1925, 1925. (f) Root, H. F. Insulin Resistance and Bronze Diabetes, *New England J. Med.* **201** 201, 1929. (g) Russell, E. Hemochromatosis, *M. J. Australia* **1** 251, 1925. (h) Shelton, J. H. The Iron Content of the Tissues of Hemochromatosis, with Special Reference to the Brain, *Quart. J. Med.* **21** 123, 1927.

3 Mann, F. C. Modified Physiological Processes Following Total Removal of the Liver, *J. A. M. A.* **85** 1472 (Nov. 7) 1925. Mann, F. C. The Liver in Relation to Carbohydrate Metabolism, *Tr. A. Am. Physicians* **50** 362, 1925. Bollman, J. L., Mann, F. C., and Magath, T. B. Studies of the Physiology of the Liver. XII. Muscle Glycogen Following Total Removal of the Liver, *Am. J. Physiol.* **74** 238, 1925.

though retarded, processes of neoglycogenesis and glycogenolysis may suffice to produce or maintain a high blood sugar level

The absence of ketonuria, even with extreme hyperglycemia and minimal dosage of insulin during the comatose terminal condition, is surprising. It is tempting, but hazardous, to connect this also with damage to the liver, which appears to be the organ chiefly concerned in the elaboration of ketone bodies<sup>4</sup>. Wakeman and Morrell<sup>5</sup> found no acetone, by qualitative test, in the urine of starving monkeys in the terminal stages of yellow fever, after prolonged periods of hypoglycemia. The stores of hepatic glycogen of these animals were extremely depleted, removing any obvious source of combustible carbohydrate. That acetonuria develops in *Macacus rhesus* monkeys when they are deprived of carbohydrate was demonstrated by the subsection of one animal to starvation.

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4 Himwich, H. E., Goldfarb, W., and Weller, A. The Effect of Various Organs on the Acetone Content of the Blood in Phlorhizin and Pancreatic Diabetes, *J. Biol. Chem.* **93**, 337, 1931.

5 Wakeman, A. M., and Morrell, C. A. Personal communication.

# HEMOCHROMATOSIS AND PURPURA

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AND

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Since Troisier's<sup>1</sup> description in 1871 of a case of "diabète sucré" with pigmentary changes, approximately 175 cases of hemochromatosis have been reported. Fourteen, or 9 per cent, of the 153 cases from the literature with data available for study, exhibited some degree of purpura, while in an additional 9 cases, or 6 per cent, hemorrhagic manifestations other than purpura developed in the course of the disease. Other authors have discussed this occurrence and have speculated on its importance in the etiology of the pigment deposits that are characteristic of the disease. In spite of this incidence of purpura in hemochromatosis, it is not generally mentioned as a frequent symptom.

The necropsy records of the department of pathology of the New Haven Hospital between 1917 and 1930 contain reports of 5 cases of hemochromatosis, all of which occurred in males. Two of the patients, at the time of admission, had purpura of such striking degree as to suggest the diagnosis of scurvy. In an earlier case reported from this hospital by Blumer,<sup>2</sup> a petechial eruption developed on the arms and legs a few hours before death.

In this report, the clinical course and pathologic observations in the two more recent cases are presented, together with a discussion of the possible explanations for purpura in hemochromatosis.

## REPORTS OF CASES

CASE 1—J M, a single, white, Irish-American restaurant worker, 44 years of age, was admitted to the New Haven Hospital on March 21, 1929.

*History*—Six months before admission his gums became sore and bled easily, and his teeth loosened. For two weeks he had experienced weakness and had become dyspneic, and a paroxysmal cough and substernal pain had developed. For one week he had raised scanty, bloodstreaked sputum. During this time he had

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1 Troisier. Diabète Sucre, Bull et mem Soc anat de Paris **14** 231, 1871, quoted by McCreery. Canad M A J **7** 481, 1917.

2 Blumer, G. Bronzed Diabetes (Hemochromatosis). Report of a Case and Review of the Literature, Proc Connecticut M Soc, 1911, p 190.

noticed reddish "pimples" over his body, which had increased in size to form bluish patches. Seven, and again five days, before admission he had experienced slight epistaxis. His legs below the knees had been swollen for a week.

His dietary history revealed a long-standing deficiency of fruits and vegetables and the fact that for six months he had eaten no meat.

*Examination*—He was a well developed, fairly well nourished man, cyanotic and hyperpneic. The lower eyelids were puffy. The gums were swollen and bleeding, with necrosis along their margins. A diffuse papulohemorrhagic rash involved mainly the extensor surfaces of the forearms and, to a lesser extent, the upper parts of the arms and thighs. On the inner aspect of both legs below the knees were extensive purplish areas. A few fading lesions were scattered over the chest and abdomen. Both legs were swollen. In the chest, there were signs of diffuse pneumonia, and the heart was moderately enlarged, without murmurs or friction rub. The systolic blood pressure was 138 mm of mercury,

TABLE 1—*Laboratory Findings in Both Cases of Hemochromatosis*

Determination	Case 1 (J. M.)	Case 2 (T. N.)
Red blood corpuscles	3,000,000 per c mm	3,100,000 per c mm
Hemoglobin (Sahli)	58 per cent	75 per cent
White blood cells	3,250 per c mm	6,250 per c mm
Neutrophils	72 per cent	59 per cent
Lymphocytes	26 per cent	41 per cent
Blood platelets	100,000 per c mm	200,000 per c mm
Clotting time	4 minutes, 30 seconds	3 minutes, 45 seconds*
Bleeding time	2 minutes, 30 seconds	3 minutes, 10 seconds†
Blood sugar	103 mg per 100 cc	139 mg per 100 cc ‡
Wassermann reaction of blood	Negative	Negative
Blood culture	No growth	No growth
Liver function test		Slight retention after 30 min §
Gastric analysis		Normal acidity#
Urine Albumin	Trace	Slightest possible trace
Sugar	Trace	Negative
Sediment	Occasional white and red blood cells	Negative

\* One month later 3 minutes, 10 seconds

† One month later 7 minutes, 10 seconds

‡ Determination made one month after admission

§ Intravenous bromsulphalein six weeks after admission

# Six weeks after admission

the diastolic, 76 mm. The abdomen was distended. Neither liver nor spleen was felt.

The laboratory findings are recorded in table 1. X-ray pictures of the chest taken on admission showed a diffuse pneumonic process with no evidence of fluid.

*Course*—The patient was digitalized. A diet high in vitamin content with orange and tomato juice was attempted, but he took nourishment poorly. On one occasion he vomited material like coffee grounds, which gave a strongly positive result in the guaiac test for blood. On the third day fluid appeared in the right knee joint. The temperature was irregular, between 100 and 103 F. After six days the purpura began to fade and the patient seemed brighter, although generalized subcutaneous edema, bilateral pleural effusion and ascites had developed. By abdominal paracentesis on the eighth day 2,500 cc of straw-colored fluid was obtained, which yielded no growth on culture. His cyanosis and respiratory difficulty progressed, and he died eight days after admission.

*Pathologic Observations*—Necropsy was performed one hour after death by Dr. George C. Wilson. The skin and sclerae were slightly icteric. Numerous dark red spots were scattered over the legs. On the thighs, these were not more than 2 mm in diameter and usually surrounded the hair follicles, but on the

ankles the hemorrhages were confluent and were from 1 to 5 cm in diameter. There was pitting edema over the extremities up to the pelvis. There were numerous hemorrhages in the skin of the scrotum. The peritoneal cavity contained fully 2 liters (2,000 cc) of pale opalescent fluid, the peritoneal surfaces were smooth. In each pleural cavity about 730 cc of clear fluid was found. A few firm, ribbon-like adhesions bound the pleural surfaces together in the regions of the apexes and bases. The pericardial sac contained about 175 cc of straw-colored fluid, in which were a few weblike masses of pale brown, semisolid material.

On microscopic examination, the skin showed a small amount of golden-yellow pigment granules, especially in the connective tissue cells adjacent to the sweat glands. The epithelial lining cells of the thyroid and prostate glands were well supplied with hemosiderin. The right knee joint was opened, but contained no blood. The bone marrow from the tibia was yellow, fatty and acellular. The brain and spinal cord were not examined. The important observations in the various other organs are recorded in table 2.

*Anatomic Diagnosis*—The primary conditions were hemochromatosis, gingivitis, anemia, multiple subcutaneous hemorrhages, fibrosis of the heart, liver and pancreas, ascites, hydrothorax, subcutaneous edema, pulmonary atelectasis, and focal pneumonia (bilateral). Subsidiary were fibrous pleural adhesions (bilateral).

CASE 2—T. N., a 42 year old American truck driver, was admitted to the hospital on May 23, 1928.

*History*—About five months before entry he noted swelling and redness of his gums and loosening of his teeth. Six weeks before entry he had a "cold" of three weeks' duration, associated with a series of night sweats and a productive cough. He experienced progressive weakness, pains in the joints and stiffness, especially involving his knees, ankles and shoulders, and observed tiny purplish spots over both shins. These spots increased in number and, for days before entry, a purplish area the size of a silver dollar appeared on the inner aspect of the left knee, which tripled its size within twenty-four hours. Except for a slight transitory remission, the pains in his joint and his weakness progressed to the point of collapse on the evening of admission. He had lost 32 pounds (14.5 Kg) within a year. For six months his diet had been deficient in fruit and green vegetables. He rarely used alcoholic liquors.

*Examination*—He was well developed and moderately emaciated. He complained of pain wherever touched. The hair of the chest, axillae and eyebrows was scanty, the hair of the head was soft and fine in texture. His skin was sallow and of a muddy shade. Petechial hemorrhages were scattered over the body and extremities. On the legs were ecchymoses from a few millimeters to about 5 cm in diameter, with multiple smaller ones surrounding the hair follicles. One large area of ecchymosis extended from the groin to below the left knee. The left knee and ankle were swollen. The right shin was covered with a raised, hard, red hematoma. There were a few conjunctival petechiae. His gums bled easily and were red and swollen with submucous hemorrhages. Many of his teeth were out, and the remaining ones were loose. There was a slight general adenopathy. The heart and lungs were not remarkable. The systolic blood pressure was 130 mm of mercury, the diastolic, 80 mm. Generalized tenderness over the upper part of the abdomen extended downward to the umbilicus. The liver was palpable 4 fingerbreadths below the costal margin in the right mammary line. It was hard and tender. The spleen was just palpable on inspiration.

TABLE 2—*Pathologic Observations in Organs in Both Cases of Hemochromatosis*

Organ	Weight, Gm		Pigment Deposits (Microscopic)		Fibrosis (Microscopic)		Miscellaneous Observations	
	Case 1	Case 2	Case 1	Case 2	Case 1	Case 2	Case 1	Case 2
Heart	410	530	In connective tissue cells, perinuclear in muscle cells	Perinuclear in many muscle cells and in lining cells of capillaries	Focal in left ventricle	Slight	Gross a few streaks of fat in myocardium Microscopic medial coronary coats split, erythrocytes between layers	Gross right side of heart dilated Microscopic many nuclei stain poorly, fat vacuoles in many muscle cells of left ventricle
Lungs	R 525 L 550	R 300 L 300	In many mononuclear phagocytes scattered in the alveoli	A little in lining cells of mucous glands and in blood vessels			Microscopic alveolar walls thick, many bronchioles desquamating, small vessels congested	Gross areas of atelectasis, moderate emphysema
Liver	1,700	2,700	Clumped intracellularly and extracellularly in fibrous tissue and hepatic cell cytoplasm	Much in hepatic cells, less in cells of smaller bile ducts, Kupffer cells and stroma	Marked portal	Marked portal, slight lobular	Gross thickened, nodular Glisson's capsule, "hobnailed" type	Gross surface granular Microscopic hepatic cells well preserved
Spleen	275	300	In many large mononuclear cells and clumped throughout	In cells of reticulum		Moderate trabecular	Gross unusually friable	Microscopic lymphocytes of malpighian corpuscles decreased in number
Pancreas	135	120	Clumped intracellularly and extracellularly in fibrous tissue, granules in acinar cells	Large amounts in acinar cells, less in islet cells	Diffusely increased	Diffusely increased	Gross individual appearance of islands of Langerhans normal Microscopic islands reduced in numbers	Gross lobular structure distinct
Kidneys	R 170 L 200	R 175 L 200	Slight, intracellularly and extracellularly in pyramidal epithelium of collecting tubules	Few traces in scattered collecting tubules	Moderate superficial		Microscopic poorly preserved, convoluted tubule cells disintegrating, blood vessels congested	Microscopic slight degree of cloudy swelling in tubular epithelium
Suprarenal glands		Both 17.5	Masses in outer cortical cells	Slight in superficial cortical cells	Slightly increased			



The laboratory findings are recorded in table 1 X-ray pictures on May 24, June 12 and Sept 17, 1928, showed no evidence of subperiosteal hemorrhages of the femora, tibiae or fibulae On June 23, 1928, a roentgenogram of the chest revealed no evidence of pneumonia or of fluid

*Course*—On large amounts of orange juice the patient began to show improvement within forty-eight hours, there was no extension of the purpura and the pains in his joints were less severe Within three weeks his red blood cell count had increased to 3,900,000 per cubic millimeter and thereafter maintained a level of 4,000,000 During the first month he had two febrile periods of a few days' duration, associated with hyperesthesia of the left upper quadrant and hepatic tenderness Except for these intervals, his temperature ranged between 98 and 100 F His purpura gradually disappeared, and he gained strength He began to show slight glycosuria, which increased in frequency and degree Four months after admission insulin was started His diabetic course is discussed in another paper<sup>3</sup>

Although he gained slowly in weight and strength, his pigmentation increased On the morning of December 12, one hour after he had apparently recovered from a mild insulin shock, treated with orange juice, he began to have transient auricular fibrillation Thereafter, in a series of hypoglycemic reactions, he repeatedly exhibited auricular fibrillation, which ceased after the administration of dextrose Three months later he had an attack typical of coronary occlusion, which lasted about one hour Within the next week auricular fibrillation became fixed, and edema developed, which was temporarily relieved by digitalization An x-ray plate of his chest showed the heart to be enlarged in all dimensions

One month before death a transient crop of petechiae developed on his hands The edema recurred with bilateral pleural effusion On May 29, 1929, he died of circulatory and hepatic failure after being in the hospital for a period of three hundred and seventy-one days

*Pathologic Observations*—Necropsy was performed two hours after death The skin of the chest and abdomen exhibited faint brownish pigmentation There was slight pigmentation of the skin of the hands Over the lower extremities from the knees down there was a marked degree of patchy, brown pigmentation, more marked anteriorly Edema was present in both lower extremities and in the foreskin and scrotum A yellow, slightly cloudy fluid was found in the peritoneal and both pleural cavities, but, except for adhesions around the spleen and between the apex of the right lung and pleura, the peritoneal and pleural surfaces were smooth The skin from the chest showed little pigment microscopically, except in a few connective tissue cells about the sweat glands The thyroid and prostate glands, the testes and many lymph nodes, especially those in the region of the pancreas and abdominal aorta, contained intracellular pigment, which stained with hemotoxylin-eosin and Perl's stains The stomach was greatly contracted, the mucosa was medium dark brown, and hemosiderin granules were demonstrated in the acidophilic and, to a slight extent, in the other epithelial cells A slight amount of pigment was found in the endothelial cells of a few small blood vessels of the skin and bone marrow The bone marrow from the right tibia was yellow, somewhat watery and aplastic The brain was not examined, there were no changes in the spinal cord The other pathologic observations are recorded in table 2

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3 Stetson, R P, and Peters, J P The Carbohydrate Metabolism in a Case of Hemochromatosis, Arch Int Med, this issue, p 226

*Anatomic Diagnosis*—The primary conditions were generalized pigmentation involving particularly the liver, pancreas spleen and lymph nodes (clinically, bronze diabetes), fibrosis of the liver, spleen and pancreas, ascites, edema of the lower extremities, and hydrothorax (bilateral) Subsidiary were hypertrophy and dilatation of the heart, fibrous adhesions of the pleura (right) and hyaline perisplenitis

#### COMMENT ON THE PATHOLOGIC OBSERVATIONS

From the standpoint of pathologic anatomy, these cases differ but little from those described in the literature, except that the cutaneous pigmentation was minimal In case 2, the pigment in practically every organ gave the blue reaction of hemosiderin with Perl's stain In the first case, the iron pigment was also widely distributed The organs involved by the pigmentation and those that showed fibrosis were the organs usually involved in this condition Although the pancreas in both patients showed a moderate degree of fibrosis, there was no hyalinization of the islands of Langerhans In the patient in case 1 there seemed to be a slight diminution in the number of these structures His diabetes was minimal This lack of correspondence between marked insular change and the clinical picture of diabetes is not unusual Sheldon,<sup>4</sup> however, noted a correlation between the severity of diabetes in hemochromatosis and the amount of pigment deposited in the pancreas Our cases suggested a similar correlation

The necropsy observations that might be correlated with the clinical scorbutic manifestations were slight In case 1, large and small extravasations of blood were seen in the skin, and the gums were spongy, dark red and receded from the teeth, which were loose No subperiosteal or joint hemorrhages were found In this case, the extent of the cutaneous hemorrhage was much greater than that described in the literature in other cases of hemochromatosis In case 2, the purpura seen on admission disappeared following antiscorbutic treatment and left little evidence of its former presence

In both necropsies, cultures were made from a number of the organs As yet, the significance of the isolation of various types of micro-organisms post mortem is not clear, and the possible relation to the clinical picture is difficult to evaluate In case 1, the general recovery of a hemolytic streptococcus is suggestive of an infection of the blood stream The elevation of temperature during the patient's last days of life can be explained on this basis The significance, if any, of the recovery of *Bacillus sporogenes* from the liver in case 2 is doubtful

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4 Sheldon, J H The Iron Content of the Tissues in Hemochromatosis, with Special Reference to the Brain *Quart J Med* **21** 123, 1927

## POSSIBLE FACTORS IN THE PURPURA OF HEMOCHROMATOSIS

Hemorrhagic manifestations other than purpura are mentioned in 6 per cent of the cases of hemochromatosis reported in the literature Bork,<sup>5</sup> in reviewing a large series of cases of hemochromatosis, found evidence of bleeding in the serous cavities, kidneys and especially the gastro-intestinal tract Many of these manifestations may be attributed to the effects of portal obstruction

The importance of the pigmentary cirrhosis of the liver as a factor in the development of the purpuric lesions of hemochromatosis must be recognized The influence of the liver on coagulation of the blood and production of fibrinogen is great, although even in the presence of extensive damage to the liver there may be little demonstrable change in either of these factors Nissen,<sup>6</sup> in an analysis of 117 cases of cirrhosis of the liver, did not record the occurrence of purpura, Rolleston<sup>7</sup> mentioned petechiae in cirrhosis, whereas Potter and Milne<sup>8</sup> stated that the hemorrhagic manifestations encountered in hemochromatosis are no more than can be observed in any series of cases of cirrhosis of the liver

In neither of the cases of hemochromatosis reported here does it seem justifiable to explain the purpura as wholly due to the hepatic damage Both patients gave a history of definite dietary deficiencies, and in both cases the clinical picture on admission demanded the consideration of scurvy in the differential diagnosis In case 1, extensive pneumonia and sepsis from a possible infection of the blood stream grafted on cirrhosis of the liver offer an adequate explanation for the development of symptomatic purpura, although the condition of the gums early in the illness and the preexisting dietary deficiency make a scorbutic element likely Certainly, a definite diminution of this patient's purpura was observed after his ingestion of limited quantities of orange and tomato juice A mild respiratory infection brought the patient in case 2 into the hospital His purpura was typically scorbutic and disappeared under antiscorbutic treatment in the face of advancing hepatic insufficiency This case offers interesting material for speculation that the development of scurvy is enhanced by hemochromatosis

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5 Bork, K Zur Lehre von der allgemeinen Hamochromatose, Virchows Arch f path Anat **269** 178, 1928

6 Nissen, H A Analysis of One Hundred and Seventeen Cases of Cirrhosis of the Liver, M Clin North America **4** 555 (Sept) 1920

7 Rolleston, H Portal Cirrhosis, Oxford Medicine, New York, Oxford University Press, 1921, vol 3, p 374

8 Potter, N B, and Milne, L S Bronzed Diabetes Report of a Case, with Special Reference to the Involvement of the Pancreas in Diabetes, Am J M Sc **143** 46, 1912

The appearance of scurvy in clinically recognized form has been infrequent in recent years. Minot,<sup>9</sup> discussing the clinical aspects of vitamin deficiencies, suggested that arteriosclerosis may enhance the development of scurvy by damage to the blood vessels, which may prevent the cells from obtaining a suitable supply of active antiscorbutic principle. Mettier, Minot and Townsend,<sup>10</sup> in a recent study of scurvy in adults, stated that "conditions due to vitamin deficiencies and due to lack of certain hormones are brought forth or intensified under various adverse conditions, for example, infectious processes, chronic fatigue and excesses of various sorts." Deposits of pigment in and around the capillaries produce definite injury to the vascular and perivascular tissues. Not only may this enhance the development of hemorrhagic manifestations by direct injury to the vascular system, but the absorption of protective substances from the blood stream by the tissues may be impaired in a way analogous to that suggested in arteriosclerosis<sup>9</sup> and susceptibility to scurvy thus be produced.

Diarrhea and other gastro-intestinal complaints have been featured in the symptomatology of many of the reported cases of hemochromatosis. In some, the finding of pigment deposits in the gastro-intestinal tract at postmortem examinations has been noted and discussed. As a result of such deposits, the absorption of antiscorbutic substances from the intestine may be impaired, and this may necessitate, to insure protection against scurvy, the ingestion of larger amounts of potent substances than a normal person would require.

#### SUMMARY

1 Purpura or hemorrhagic manifestations have been observed in 15 per cent of the 153 cases of hemochromatosis studied in the literature.

2 The clinical and pathologic observations in 2 cases of hemochromatosis with initial symptoms of scurvy are reported, and the pathologic observations are discussed.

3 Possible mechanisms for the development of the hemorrhagic manifestations of hemochromatosis are discussed, and it is suggested that hemochromatosis may predispose the subject to scurvy.

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<sup>9</sup> Minot, G. R. Some Fundamental Clinical Aspects of Deficiencies, *Ann Int Med* **3** 216, 1929.

<sup>10</sup> Mettier, S. R., Minot, G. R., and Townsend, W. C. Scurvy in Adults, Especially Effect of Food Rich in Vitamin C on Blood Formation, *J. A. M. A.* **95** 1089 (Oct 11) 1930.

# IMPORTANCE OF HEPATOMEGALY AND SPLENO- MEGALY IN DIFFERENTIAL DIAGNOSIS

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The liver and the spleen show greater variations in size under abnormal states than any other organs of the body. Livers weighing from two to four times the normal and spleens from five to twenty times the normal are not infrequently encountered. Since these organs are so situated that on enlarging they soon become palpable, definite enlargements become helpful in differential diagnosis. Unfortunately, moderate enlargements are not so helpful in diagnosis, because they are encountered under such a large variety of conditions. However, massive enlargements—splenomegaly and especially hepatomegaly—are caused by relatively few diseases, and the knowledge of this fact will greatly aid in arriving at a correct differential diagnosis by precluding from consideration a large group of diseases that could scarcely be the basis of such enlargement.

In order to establish as accurately as possible the conditions that may give rise to large livers and spleens the present study was undertaken.

## MATERIAL

It consists of the protocols of 12,000 autopsies performed during the past ten years between Jan 1, 1921, and Jan 1, 1931 (table 1). It must be understood at the outset that such autopsy material represents a group of cases that does not furnish an accurate cross-section of the sick population of the country or even of the entire local community. Nevertheless, conditions that would not be encountered in this study should be infrequent, since this series represents the autopsies performed at most of the hospitals in Minneapolis, including the University Hospital and the Minneapolis General Hospital, as well as those performed outside these hospitals. Included also are all the coroners' cases and

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From the Department of Medicine, University of Minnesota

Delivered before the Minnesota Academy of Medicine, St Paul, Minn., Nov 11, 1931

The material for this study was obtained in the Department of Pathology of the University of Minnesota, through the permission of Dr E. T. Bell

many of the autopsies performed in St Paul in and outside of the hospitals. The entire mass of material was carefully scrutinized and tabulated as may be seen in tables 2 and 3. Included in these tables are those conditions that produce livers weighing over 2,200 Gm and spleens weighing over 300 Gm. The basis for this arbitrary choice of figures is the fact that livers and spleens generally become palpable when they reach such proportions. The average normal weight of the adult liver is between 1,500 and 1,900 Gm and of the adult spleen

TABLE 1—*Major Causes of Death from Jan 1, 1921, to Jan 1, 1931*

Total number of autopsies performed	12,134
Autopsies on infants and children, not reviewed	2,400 (circ.)
Total number reviewed	9,280
Records incomplete	450 (circ.)
Total number listed	7,857

Heart disease	1,582
Malignant tumors	1,083
Accidents	1,042
Pneumonia	808
Tuberculosis (exclusive of cases with amyloidosis)	317
Cerebral hemorrhage (apoplexy)	241
Acute and chronic alcoholism	251

Year	Autopsies	Alcoholism	Per Cent
1921	574	5	0.87
1922	649	13	2.00
1923	849	14	1.70
1924	860	22	2.50
1925	1,061	18	1.70
1926	1,161	33	2.80
1927	1,353	30	2.20
1928	1,736	29	1.70
1929	1,909	35	1.80
1930	1,952	52	1.70

Meningitis	229
Cirrhosis of the liver	129
Nephritis	92
Diabetes	56
Abortion	55
Puerperal sepsis	52
Hodgkin's disease	37
Typhoid fever	24

between 90 and 200 Gm. A biometric statistical study of a larger series of cases is in preparation to determine the range of weights of these organs in different diseases. Curves representing normal weights derived from the study of cases of accidental death from this series are soon to be published by Dr. Edith Boyd, of the Department of Child Welfare of the University of Minnesota. Only adults are included in our study.

#### INCIDENCE AND DEGREE OF HEPATIC SPLENIC ENLARGEMENTS IN VARIOUS DISEASES

Tables 2 and 3 show the distribution of enlargements of the liver and the spleen among the various diseases and in the different weight

TABLE 2—*Livers Weighing 2,200 Gm and Over*

Total Number of Cases	Primary Cause of Death	Cases with Enlargement of Liver			Cases with Enlargement of Liver and Spleen			Cases with Enlargement of Spleen			Hepatic Weight in 100 Gm., Number of Cases											
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	22 to 25	25 to 30	30 to 35	35 to 40	40 to 45	45 to 50	50 to 55	55 to 60	60 to 65	65 to 70	70 to 70+		
1	Heart disease	128	8.5	62	4.1	158	10.4	81	40	7	7	7	7	10	5	6	2	4	3	3		
2	Tumors	153	14.1	35	3.2	72	6.7	62	33	21	21	21	6	9	4	5	1	3	3	3		
A	Carcinoma	145	14.6	34	3.4	66	6.6	61	32	6	6	6	2	4	3	2	2	2	2	2		
(a)	Stomach	35	16.5	6	2.8	7	3.3	12	4	6	2	1	3	2	1	2	2	2	2	1		
(b)	Pancreas	24	30.0	3	3.7	10	12.5	8	7	3	3	1	1	2	1	2	2	2	2	1		
(c)	Colon	7	9.7	1	1.3	3	4.1	1	3	1	1	1	1	1	1	1	1	1	1	1		
(d)	Lung	11	17.7	3	4.8	5	8.0	4	4	1	1	1	1	1	1	1	1	1	1	1		
(e)	Rectum	3	5.6	1	1.8	4	7.5	7	3	2	2	2	2	2	2	2	2	2	2	2		
(f)	Kidney	12	29.2	5	12.1	5	12.1	1	1	1	1	1	1	1	1	1	1	1	1	1		
(g)	Breast	4	8.1	1	2.04	2	4.08	4	4	4	4	4	4	4	4	4	4	4	4	4		
(h)	Gallbladder and biliary ducts	8	28.5	1	3.9	4	14.3	4	4	4	4	4	4	4	4	4	4	4	4	4		
(i)	Bladder	4	10.0	1	2.5	1	2.5	4	4	4	4	4	4	4	4	4	4	4	4	4		
(j)	Ovary	7	19.4	1	2.7	2	5.4	4	4	4	4	4	4	4	4	4	4	4	4	4		
(k)	Testicle	3	17.6	1	5.8	2	11.6	2	2	2	2	2	2	2	2	2	2	2	2	2		
(l)	Liver	4	22.2	2	11.1	2	11.1	2	2	2	2	2	2	2	2	2	2	2	2	2		
(m)	Uterus	3	3.7	2	4	4	5.0	3	3	3	3	3	3	3	3	3	3	3	3	3		
(n)	Prostate	3	4.5	2	3.18	3	4.5	3	3	3	3	3	3	3	3	3	3	3	3	3		
(o)	Esophagus	36	2.7	1	2.7	1	2.7	1	1	1	1	1	1	1	1	1	1	1	1	1		
(p)	Miscellaneous	16	15.8	5	4.9	11	10.9	9	9	9	9	9	9	9	9	9	9	9	9	9		
B	Melanoma	7	38.8	1	5.5	4	22.2	4	4	4	4	4	4	4	4	4	4	4	4	4		
C	Sarcoma	1	1.3	2	2.6	2	2.6	1	1	1	1	1	1	1	1	1	1	1	1	1		
3	Pneumonia	110	13.6	26	3.2	50	6.1	61	39	8	8	8	2	2	2	2	2	2	2	2		
4	Miscellaneous acute infections	87	12.7	26	3.8	90	13.1	55	26	5	5	5	1	1	1	1	1	1	1	1		
5	Trauma	613	5.3	6	0.99	17	2.7	22	7	3	3	3	1	1	1	1	1	1	1	1		
6	Fracture of skull	429	7.2	1	0.23	7	1.6	21	10	2	2	2	1	1	1	1	1	1	1	1		
7	Peritonitis	364	6.5	7	1.9	24	6.5	18	4	2	2	2	1	1	1	1	1	1	1	1		
8	Suicide	347	8.3	5	1.4	17	4.8	19	7	3	3	3	1	1	1	1	1	1	1	1		
9	Tuberculosis	318	3.4	9	2.8	37	11.3	8	2	1	1	1	1	1	1	1	1	1	1	1		
10	Cerebral hemorrhage and embolism	241	11.6	6	2.4	17	7.05	19	8	3	3	3	1	1	1	1	1	1	1	1		
11	Meningitis	229	5.6	7	3.05	12	5.2	9	3	1	1	1	1	1	1	1	1	1	1	1		
12	Acute and chronic alcoholism	231	22.0	3	1.3	6	2.6	21	16	12	12	12	3	3	3	3	3	3	3	3		
13	Undetermined	146	4.1	1	0.68	8	5.4	5	5	1	1	1	1	1	1	1	1	1	1	1		
14	Cirrhosis	129	29.6	21	16.2	69	53.4	19	13	4	4	4	1	1	1	1	1	1	1	1		
15	Septicemia	102	17.6	10	9.8	32	31.3	12	6	1	1	1	1	1	1	1	1	1	1	1		
16	Glomerular nephritis	92	4.3	1	1.08	8	8.6	9	1	1	1	1	1	1	1	1	1	1	1	1		
17	Amyloidosis	89	11.2	8	9.0	12	13.5	1	2	2	2	2	2	2	2	2	2	2	2	2		
18	Subacute bacterial endocarditis	87	27.5	24	27.5	74	85.05	15	6	3	3	3	4	4	4	4	4	4	4	4		
19	Pernicious anemia	67	8.9	5	7.1	14	20.8	1	1	1	1	1	1	1	1	1	1	1	1	1		
20	Leukemia	64	46.8	29	45.3	49	76.5	9	11	4	4	4	4	4	4	4	4	4	4	4		
21	Diabetes	56	10.7	2	3.5	5	8.9	5	5	1	1	1	1	1	1	1	1	1	1	1		
22	Abortion	53	10.8	6	10.8	9	16.3	4	1	1	1	1	1	1	1	1	1	1	1	1		
23	Puerperal sepsis	52	23.07	9	17.3	21	40.3	7	3	2	2	2	2	2	2	2	2	2	2	2		
24	Hodgkin's disease	37	16.2	6	16.2	23	62.1	3	1	1	1	1	1	1	1	1	1	1	1	1		
25	Typhoid fever	21	16.6	4	16.6	8	33.3	3	3	3	3	3	3	3	3	3	3	3	3	3		
26	Gumma	7†	57.1	2	33.3	4	66.6	1	2	1	2	1	2	1	2	1	2	1	2	1		

\* Exclusive of eighty seven cases of subacute bacterial endocarditis

† Exclusive of four cases of congenital syphilis

TABLE 3—*Spleen Weighing 300 Gm and Over*

Primary Cause of Death	Total Number of Cases	Cases with Enlargement of Spleen		Spleen Weight in Grams, Number of Cases																															
		Number	Per Cent	300 to 350		350 to 400		400 to 450		450 to 500		500 to 550		550 to 600		600 to 650		650 to 700		700 to 750		750 to 800		800 to 900		900 to 1,000		1,000 to 1,200		1,200 to 1,400		1,400 to 1,600		1,600 Plus	
				to 300	to 350	to 350	to 400	to 400	to 450	to 450	to 500	to 500	to 550	to 550	to 600	to 600	to 650	to 650	to 700	to 700	to 750	to 750	to 800	to 800	to 900	to 900	to 1,000	to 1,000	to 1,200	to 1,200	to 1,400	to 1,400	to 1,600	Plus	
1 Heart Disease	1,505	158	10.4	76	14	15	10	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
2 Tumors	1,083	72	6.7	31	14	11	5	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
A Carcinoma	990	66	6.9	29	14	11	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
(a) Stomach	211	7	3.3	1	1	2	1																												
(b) Pancreas	80	10	12.5	6	6	1																													
(c) Colon	72	3	4.1	2	2																														
(d) Lung	62	5	8.0	3	3																														
(e) Rectum	33	4	7.5	2	2																														
(f) Kidney	41	5	12.1	2	2																														
(g) Breast	49	2	4.0	2	2																														
(h) Gallbladder and biliary ducts	28	1	4.3	1	1																														
(i) Bladder	40	1	2.5	1	1																														
(j) Ovary	36	2	5.4																																
(k) Testicle	17	2	11.7																																
(l) Liver	18	2	11.1																																
(m) Uterus	80	4	5.0	1	1																														
(n) Prostate	66	3	4.5																																
(o) Esophagus	36	1	2.7																																
(p) Miscellaneous	101	11	10.8	1	1	3	2																												
B Melanoma	18	4	22.2	1	1																														
O Sarcoma	75	2	2.6	1	1																														
3 Pneumonia	808	50	6.1	21	9	17	13	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
4 Miscellaneous acute infections	682	90	13.1	36	17	13	12	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
5 Trauma	613	17	2.1	7	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
6 Fracture of skull	429	7	1.6	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
7 Peritonitis	364	24	6.5	14	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
8 Suicide	347	17	4.8	10	2	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
9 Tuberculosis	317	36	11.3	15	12	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
10 Cerebral hemorrhage and embolism	241	17	7.05	9	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
11 Acute and chronic alcoholism	231	6	2.6	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
12 Meningitis	229	12	5.2	6	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
13 Undetermined	146	8	5.4	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
14 Cirrhosis	129	69	54.7	17	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	
15 Septicemia	102	32	31.3	16	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
16 Glomerular nephritis	92	8	8.6	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
17 Amyloidosis	89	12	13.5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
18 Subacute bacterial endocarditis	87	74	85.05	16	11	11	8	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
19 Pernicious anemia	67	14	20.8	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
20 Leukemia	64	49	76.5	6	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
21 Diabetes	56	5	8.9	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
22 Abortion	55	9	16.3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
23 Puerperal sepsis	52	21	40.3	9	3	4	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
24 Hodgkin's disease	37	23	62.1	2	2	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
25 Typhoid fever	24	8	33.3	2	2	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
26 Gumma*	7	4	57.1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
27 Histoplasmosis	1	1	100.0																																

\* Exclusive of four cases of congenital syphilis

† 1,620, 1,650, 1,700, 1,750, 1,850, 2,200, 2,350, 2,400, 2,750, 2,860, 3,760



groups The weights as recorded are in many instances considerably less than the weights of the organs in the body during life, because of the loss of blood content It should be observed that this series does not include certain other diseases found in tropical and subtropical countries which may also produce hepatomegaly and splenomegaly, such as malaria, kala-azar, and amebic abscesses of the liver Still another group of diseases is not present in this list, the absence of which cannot be so readily explained Not a single case of Gaucher's disease was found, that peculiar, rare disease characterized by "foamy" enlarged cells of the reticulo-endothelial system of the body which may produce spleens weighing as much as 8,000 Gm There is also a striking absence of congenital hemolytic jaundice and polycythemia vera (Osler's disease, Vaquez' disease), and there is only one case of Banti's disease In this case, the spleen weighed 780 Gm, but at autopsy there were such

TABLE 4—*Banti's Splenomegaly (Postoperative Spleens)*

No	Splenic Weight, Gm *	Comment†
Op 22 36	?	Spleen extended to navel, histologically, Banti's disease
Op 22 457	?	Histologically, Banti's disease
Op 22 474	545	In boy 14 years old, histologically, Banti's disease
Op 22 590	?	Histologically, Banti's disease
Op 24 82	640	Marked fibrosis of reticulum, histologically, Banti's disease
Op 25 842	800	Splenomegaly, leukopenia
Op 28 669	610	Banti's disease, with cirrhosis of liver
Op 28 799	?	Marked fibrosis
Op 30-204	1,200	Histologically, Banti's disease, later, blood changes of lymphatic leukemia developed, still later, diagnosis became uncertain ‡

\* No weights given in half of the cases, none of the spleens very large

† Last case definitely not Banti's disease

‡ In group of spleens operated on were included one from a patient who had Gaucher's disease and two from patients who had hemolytic jaundice, the weights of these spleens are not given

marked perisplenitis and perihepatitis—probably the result of the numerous tappings for ascites—that on account of the marked surface inflammation the case was included in the miscellaneous group One other case of Banti's disease was not included because there had been a splenectomy performed three years previously, and the weight of the spleen could not be obtained It is undoubtedly true that many cases clinically diagnosed as Banti's disease are really cases of aleukemia, cirrhosis of the liver, thrombosis of the splenic vein, etc In order to determine the average weight of Banti's spleens, the records of the spleens operated on were gone over, and the findings are indicated in table 4 The chief characteristic of this disease is the secondary anemia with leukopenia together with an enlarged firm spleen that histologically shows marked fibrosis

It will be noted from table 2 that enlarged livers weighing less than twice the normal weight are found in such a large variety of conditions that by themselves they prove of little value for differential diagnosis

It is only when a true hepatomegaly of 4,000 Gm or over is encountered—a liver that on the average reaches down to the level of the umbilicus—that the enlargement becomes significant. The same holds true for the spleens weighing below 550 Gm. A spleen weighing 600 Gm is easily palpable, since it usually extends down to about 4 or 5 cm below the costal margin.

IMPORTANCE OF HEPATIC AND SPLENIC ENLARGEMENTS IN  
DIAGNOSIS OF VARIOUS DISEASES (COMMENT  
ON TABLES 2 AND 3)

*Heart Disease*—In heart disease the condition of the liver is of little significance. The enlargement of the liver is only moderate, being the result of acute or chronic passive congestion. The spleen is also only moderately enlarged; in very few cases it reaches a size of from 600 to 900 Gm. The enlargement is due, as in the case of the liver, to

TABLE 5—*Hepatomegaly*

	Total Number of Cases	Cases in Which Liver Weighed 4,000 Gm or More*	
		Number	Per Cent
1 Carcinoma	990	25	2.5
(a) Stomach	211	11	5.2
(b) Pancreas	80	6	7.5
(c) Liver	18	2	11.1
(d) Lung	62	2	3.2
(e) Rectum	53	2	3.8
(f) Colon	72	1	1.4
(g) Miscellaneous (vulva)	101	1	1.0
2 Melanoma	18	5	27.0
3 Leukemia	64	2	3.1
4 Amyloidosis	89	2	2.2
5 Hodgkin's disease	37	1	2.7

\* Of the thirty-five cases in which the liver weighed more than 4,000 Gm, twenty-five, or 71.4 per cent, were due to metastatic carcinoma, five, or 14.3 per cent, were due to melanoma, two, or 5.7 per cent, were due to leukemia and one to amyloid, and one, or 2.9 per cent, was due to Hodgkin's disease. Eighty-six per cent were therefore due to carcinoma.

passive congestion with mild replacement fibrosis, the so-called cyanotic induration. Since the cause of these hepatic and splenic enlargements is generally easily recognized, such enlargements offer no difficulties in diagnosis. It might be pointed out, however, that the enlarged liver in this condition means passive congestion from congestive heart failure, and therefore is an important finding to substantiate the diagnosis of cardiac decompensation.

*Cancer*—As may be seen from table 5, malignant tumors comprise the principal source for hepatomegaly, producing the enlargement in 86 per cent of the livers weighing 4,000 Gm and over. It is to be noted that sarcoma is not included in this table because sarcoma produces enlargement neither of the liver nor of the spleen. Melanoma, on the other hand, was responsible not only for the enlargement in some of

the most massive of the livers, but also for the greatest incidence, 39 per cent, of such enlargement, 27 per cent of the livers affected by melanoma weighed over 4,000 Gm. In the matter of metastases, therefore, melanoma resembles carcinoma, and this characteristic lends great support to those authorities who insist that melanoma should be classified as melanocarcinoma and not as melanosarcoma.

Of the carcinomas proper, those of the stomach produced the largest number of hepatomegalies. It will be seen from table 5 that carcinomas of the gastro-intestinal tract and its appendages (pancreas, liver) almost exclusively produce these very large livers. The only exceptions were two carcinomas of the lung, and one carcinoma of the vulva. Tumors of the prostate, uterus and breast practically never produce true hepatomegalies.<sup>1</sup>

A striking feature of hepatic enlargement in some cases of metastatic carcinoma is the rapidity of its development. In case 1, a massive enlargement developed in about a month. In case 2 a huge enlargement occurred in less than three weeks. An explanation for the rapid increase in size was found at the postmortem examination in case 1 (see a later paragraph), large masses of infiltrated lymph nodes surrounding the portal vein were seen to have infiltrated and ruptured into this blood vessel and thus produced miliary metastases throughout the liver. Naturally such a spread would result in very rapid enlargement. In several of our cases the liver enlarged threefold within a period of a few weeks.

Another important fact to remember is that not infrequently carcinomas and especially carcinomas of the liver may cause very high septic temperature similar to that seen in cases of portal thrombosis or hepatic abscess. Case 2 is a striking illustration of this. The fever in this case was so pronounced that we were convinced that the enlargement was on an infectious basis. We were rather disappointed not to find pus after a number of attempted aspirations through puncture. We should, however, have known at the outset that the size of the liver, which extended several fingerbreadths below the umbilicus, practically excluded the possibility of the enlargement being due to an infectious process. In five of the seven cases of hepatic abscesses in the present study (included under the miscellaneous group), the weights ranged between 2,000 and 2,500 Gm, one liver, owing to amebic abscess, weighed 2,800 Gm, the seventh case was somewhat complicated in that there was acute pylephlebitis superimposed on a chronic hepatic condition, probably biliary

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1 Since writing this paper, a case has come to autopsy in which there was found a very large nodular liver, weighing 4,350 Gm, riddled with cancer nodules, the primary growth of which was in the prostate, whence it had broken through into the bladder. This is the only case encountered of a hepatomegaly from such a primary location. In this case, also, the liver enlarged very rapidly.

cirrhosis This liver was riddled with abscesses and weighed 3,800 Gm We are therefore justified in concluding that inflammatory and suppurative conditions in the liver seldom if ever need to be considered when there is definite hepatomegaly present, even when accompanied by high fever

In striking contrast to the relative frequency of enlargement of the liver in cases of tumors is the almost complete absence of any such enlargement in the spleen Of over 1,000 cases of malignant growths, only 7, or less than 1 per cent, showed any definite splenic enlargement In one of these, the increase was due to a tumor metastasis, in another, to extension of an abscess from the colon, in the rest, the enlargement resulted principally through congestion from pressure of the enlarged lymph nodes on the splenic vein This relative absence of splenic enlargement in malignant conditions is an important fact to remember

In seventy-five cases of sarcoma there was no single occurrence of hepatic enlargement, and in only one case did the spleen reach a weight of 450 Gm The absence of hepatic enlargement in sarcoma may therefore be used for differential diagnosis from carcinoma

*Acute Infections*—The acute infections—pneumonia, peritonitis, meningitis and typhoid fever—present only moderate enlargements of the liver and spleen In these instances, the enlargement of the liver is due principally to cloudy swelling, the spleens are enlarged from acute congestion and splenitis In the case of typhoid fever there is moderate enlargement of both liver and spleen in 16 per cent of the cases and of the spleen alone in 33 per cent (table 6) The miscellaneous acute infections were associated with several rather large spleens, five of which weighed between 900 and 1,400 Gm These enlargements were due to acute splenitis The hepatic weights in this group did not go above 3,500 Gm

*Traumatic Conditions*—Fractured skulls and other traumatic conditions and cerebral hemorrhage produce moderate enlargement of both liver and spleen, and this is the result of acute congestion, cloudy swelling and fatty changes It is very likely that in a considerable number of cases included in the group of accidents the enlargement of the liver was a result of fatty changes due to alcoholism About the same may be said in the cases of suicides

*Tuberculosis*—This disease presents nothing significant, except that it is the most important cause of amyloidosis Primary tuberculosis of the spleen may produce a very large organ, but this condition is extremely rare

*Alcoholism*—Acute and chronic alcoholism is responsible for 22 per cent of the enlarged livers The enlargement is caused principally by fatty changes The spleen seems practically unaffected If we may be

permitted to digress, it might be pointed out that the number of cases of acute and chronic alcoholism (table 1) has not been at all reduced by prohibition, but has actually increased. From three such cases in 1919 and two in 1920, there has been a progressive increase to a total of thirty-three cases, or 28 per cent of the number of autopsies performed, in 1926.

In the group of undetermined cases there was one case in which the spleen weighed over 1,200 Gm. This was a case of abscess of the abdominal wall. The pathologic condition seemed to be simple acute splenitis.

*Cirrhosis of the Liver*—Cirrhosis of the liver is an interesting subject, since the study reveals the fact that contrary to the general belief there is practically no true hepatomegaly in this condition. At autopsy, in about one half of the cases, the livers presented were smaller than

TABLE 6—Combined Hepatic and Splenic Enlargement

Primary Cause of Death	Combined Hepatic and Splenic Enlargement, per Cent	Enlargement of Liver, per Cent	Enlargement of Spleen, per Cent
Leukemia	45.3	46.8	76.5
Gumma	33.3	66.6	57.1
Subacute bacterial endocarditis	27.5	27.5	85.0
Puerperal sepsis	17.3	23.0	40.3
Typhoid fever	16.6	16.6	33.3
Hodgkin's disease	16.2	16.2	62.1
Cirrhosis of liver	16.2	28.6	34.7
Abortion	10.8	12.7	16.3
Septicemia	9.8	17.6	31.3
Amyloidosis	9.0	13.5	11.2
Perniciou anemia	7.4	8.9	20.8
Melanoma	5.5	22.2	38.8

normal and in the other half the livers were either normal in size or only moderately enlarged. In only 28 per cent, the livers weighed more than 2,200 Gm., and not one weighed more than 3,700 Gm. It is interesting to note that in case 1, in which the liver extended far below the umbilicus, and at autopsy weighed 6,150 Gm., the condition had been diagnosed clinically by excellent men as probable cirrhosis of the liver. The very size of the liver, together with its rapid enlargement, should have at once precluded such a diagnosis. One should remember, however, that in cirrhosis the liver is usually in the atrophic stage when examined at autopsy, and that in most cases it has passed through the stage of considerable enlargement, this enlargement, however, seldom approaches the massive proportions found in cancer. The spleen in this condition shows a greater tendency to enlargement, weighing more than 300 Gm. in 34 per cent of the cases and over 600 Gm. in 11 per cent of the cases (tables 3 and 7). Many cases of splenomegaly erroneously diagnosed Banti's disease are probably due to cirrhosis of the liver.

*Septicemia, Puerperal Sepsis and Abortion*—These conditions may be grouped together with reference to enlargement of the liver and

spleen The liver shows very moderate enlargement, rarely over 3 500 Gm The spleen shows a more definite enlargement Occasionally spleens are found weighing over 600 Gm The enlargement is due to acute splenitis together with congestion These conditions are summarized in tables 6 and 7 Glomerulonephritis occasionally shows slight enlargement of these organs, but the reason for that is not clear In one case the spleen weighed over 600 Gm This case, however, had an associated very severe anemia, the type of which was undetermined

*Amyloidosis*—An important group in this study is that of livers and spleens enlarged as a result of amyloidosis When there is present a

TABLE 7—*Splenomegaly*

Cause of Death	Total Number of Cases	Number in Which Spleen Weighed		Diagnostic Importance*
		600 Gm	1,000 Gm	
Leukemia	64	35	19	4 plus
Subacute bacterial endocarditis	87	19	1	2 plus
Cirrhosis of liver	129	14		2 plus
Hodgkin's disease	37	9	2	3 plus
Heart disease	1,505	8		
Acute infections	682	8	2	1 plus
Osteosarcoma	990	6	1	
Pneumonia	808	4		
Septicemia	102	4		1 plus
Amyloidosis	89	3	2	2 plus
Abortion	55	3		1 plus
Trauma	1,042	2		
Pernicious anemia	67	2		
Puerperal sepsis	52	2		
Melanoma	18	1		
Tuberculosis†	317	1		
Gumma of liver	7	1		1 plus
Typhoid fever	24	1		
Peritonitis	36	1		
Nephritis	92	1		
Histoplasmosis	1	1	1	
Undetermined	146	1	1	

\* Splenomegaly is of definite importance for diagnosis in leukemia, Hodgkin's disease, amyloidosis, subacute bacterial endocarditis, cirrhosis of the liver and gumma of the liver

† Exclusive of cases with amyloidosis

combination of enlargement of spleen and liver and albuminuria, together with a suppurative lesion (tuberculosis, chronic empyema, chronic osteomyelitis) or gumma, amyloid is probably present Cases 3 illustrates this point Tables 5, 7 and 8 show that some of the very great enlargements of liver and spleen may be caused by this condition

*Subacute Bacterial Endocarditis*—This condition produces moderate enlargement of liver and spleen, both showing lesions in 27 per cent of the cases, the spleen itself being enlarged in 85 per cent of the cases (table 6) The splenic enlargement is a result of acute splenitis, frequently associated with infarctions A sudden, sharp pain in the left hypochondrium that persists for some time in a case in which a cardiac condition obtains should strongly suggest subacute bacterial endocarditis, especially if fever is present There is no type of acute infection that so frequently shows enlargement of the spleen or of both liver and spleen

as this type of endocarditis (table 6) The enlargement of the spleen therefore is an important finding for the diagnosis of this condition

*Pernicious Anemia*—Pernicious anemia produces only slight enlargement of the liver and spleen The enlargement is due principally to overactivity in the blood pigment metabolism and to increased storage of the blood pigments

*Leukemia*—Leukemia forms the most important group in the enlargement of these organs, especially of the spleen Under leukemia are included the lymphatic, myelogenous and mixed types, as well as the aleukemic states of these conditions Lymphatic leukemia is generally associated with enlargement of the peripheral lymph nodes In a general way, the spleen shows more massive enlargement in myelogenous leukemia than in lymphatic Except in aleukemic states and the rare

TABLE 8—*Splenomegaly (1,000 Gm or More)*

Primary Cause of Death	Cases in Which Spleen Weighed 1,000 Gm or More		Cases in Which Spleen Weighed 1,400 Gm or More*	
	Number	Per Cent of Total	Number	Per Cent of Total
Leukemia	19	65.0	11	78.6
Hodgkin's disease	2	7.0	1	7.1
Amyloidosis	2	7.0	1	7.1
Acute infections	2	7.0		
Subacute bacterial endocarditis	1	3.5		
Carcinoma	1	3.5		
Histoplasmosis	1	3.5	1	7.1
Undetermined	1	3.5		
Total number of cases	29		14	

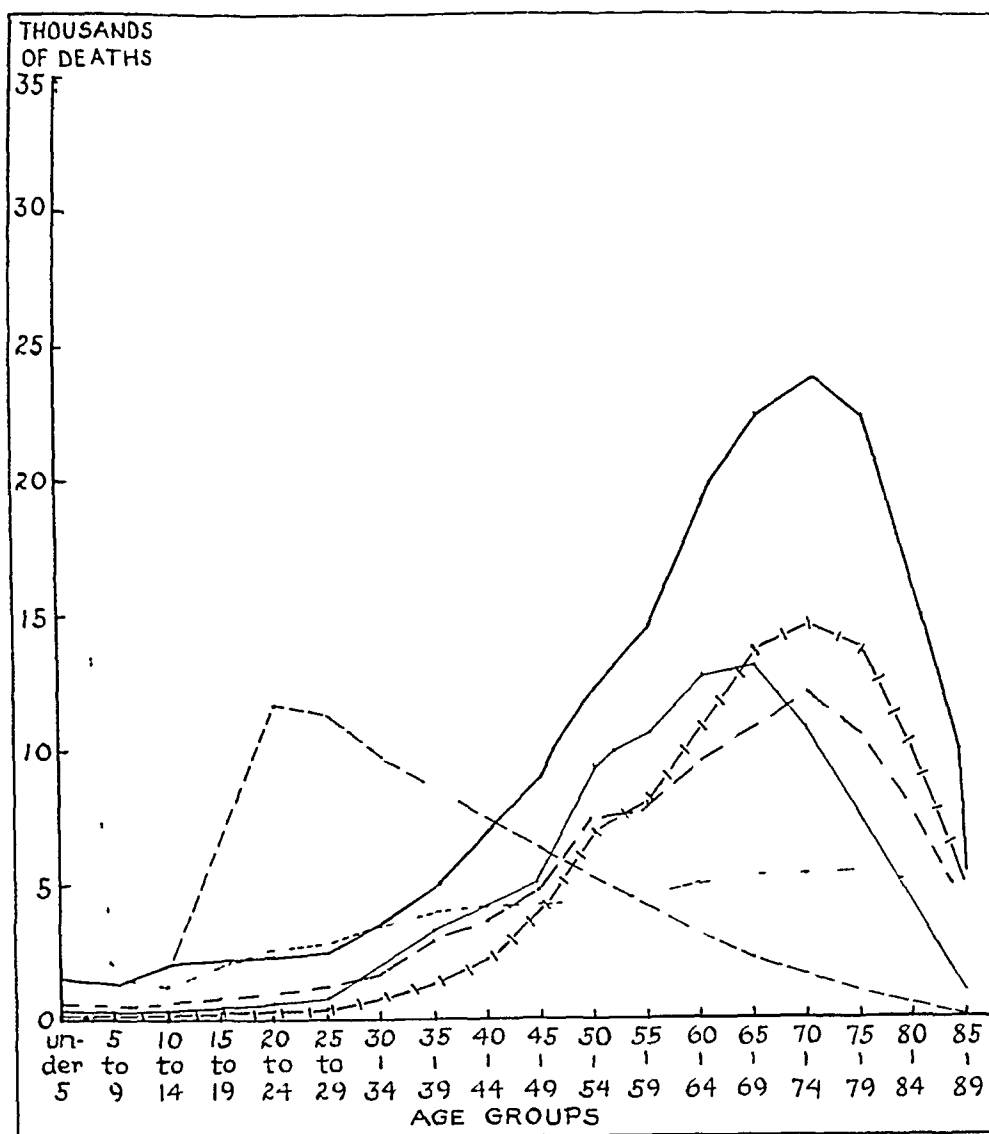
\* Seven spleens weighed over 2,000 Gm each, the largest weighing 3,760 Gm, or more than twice the weight of the normal liver These were all from patients who had leukemia

cases of benign lymphadenoses, a definite diagnosis can readily be established by careful examination of the blood The liver is only moderately enlarged, rarely above 4,000 Gm In one case, however, it reached the enormous weight of 7,800 Gm The striking feature of this group of cases is the marked splenomegaly Of the sixty-four cases, forty-nine, or 76 per cent, showed splenic enlargement, and nineteen, or 30 per cent, of the spleens weighed over 1,000 Gm (table 8)

In the entire series, seven spleens weighed 2,000 Gm and over, and in all of these the increase was due to leukemia The largest spleen weighed 3,760 Gm, or more than twice the weight of a normal liver and about twenty-five times the weight of a normal spleen Tables 7 and 8 show how leukemia is foremost in causing splenic enlargement, and table 6 shows that it produces also the most frequent combined enlargements

*Diabetes*—Diabetes shows no significant hepatic or splenic enlargement

*Hodgkin's Disease*—This disease forms another interesting group for study. In a total of thirty-seven cases, nine of the spleens weighed over 600 Gm, and two over 1,000 Gm each. The importance of this disease in splenomegaly is second only to that of leukemia (table 8). The splenic and hepatic enlargements are due to nodular infiltrations



Deaths from heart disease and other principal causes in the United States Registration Area in 1924: heavy solid line, heart disease; light solid line, cancer; dotted line, pneumonia; dash line, tuberculosis; dash-dot line, nephritis; dash-bar line, cerebral hemorrhage.

with the characteristic granulomatous (Hodgkin's) tissue. The liver shows moderate enlargement in some of the cases. Usually this disease presents marked increase in the size of the superficial and deep lymph nodes, a biopsy of which generally establishes the diagnosis. In a few rare cases there are no glandular enlargements, but there develops



an undulant type of fever that is characteristic. In this so-called Pel-Ebstein type of Hodgkin's disease a large spleen can often be palpated.

*Gummas*—Gummas are rare, and gummas of the liver are still more infrequent. Only seven cases were found in this series, exclusive of four cases of congenital cirrhosis of the liver. Of the seven cases, four showed hepatic enlargements between 2,200 and 3,500 Gm. The spleen was enlarged in four cases, and in one it weighed over 1,000 Gm. In about one third of the cases, both spleen and liver were enlarged. It is important to remember, therefore, that gumma of the liver is rare and, when present, does not produce massive hepatomegaly.

*Histoplasmosis*—There was one unusual case of histoplasmosis in which the spleen was enormously enlarged, weighing 1,450 Gm. Little need be said about this condition, because of its extreme rarity.

#### GENERAL COMMENT

This statistical analysis of all the cases presenting enlarged livers in our series demonstrates that marked hepatomegaly of 4,000 Gm. or over is present in only a few conditions. This is clearly shown in table 5. By far the greatest number of hepatomegalies encountered were secondary to carcinoma of the stomach, but the greatest percentage from any one condition is from melanoma, which ranks third in actual frequency. This table shows graphically how few are the conditions that can produce true hepatomegaly, and also which conditions should be considered for differential diagnosis whenever a massively enlarged liver presents itself. Usually there is little difficulty in differentiating between Hodgkin's disease, amyloidosis, leukemia, melanoma and carcinoma. When a very large liver is encountered, and the first four conditions can be ruled out, then it is imperative to make a careful study in order to locate the primary site of the carcinoma. Difficulties may arise in determining definitely where the primary lesion is. However, a careful history and physical examination together with roentgen studies should seldom leave one in doubt as to the exact location of the primary tumor.

The number of conditions to be considered in cases of splenomegaly is greater than in those of hepatomegaly. Table 7 shows the relative importance of the spleen in differential diagnosis. According to this table, the spleen is rated in leukemia as four plus, in Hodgkin's disease as three plus, in amyloidosis, cirrhosis of the liver and subacute bacterial endocarditis as two plus, and in gumma, septicemia, abortion and miscellaneous acute infections as one plus. Very massive splenic enlargements, the spleen reaching the pelvic brim, are due almost exclusively to leukemia. Occasionally, however, amyloidosis, Hodgkin's disease and acholuric jaundice may produce very great enlargement of the spleen. An extremely rare condition that may produce a huge splenic increase is

cyst of the spleen Not a single case was encountered in this series In our study of reports of autopsies, together with the operative records, true Banti's disease appears to be rare, and the splenic enlargement in this disease in no case was great (table 4) From our observation it would seem that Banti's disease is altogether too frequently diagnosed when an enlarged spleen is present Gaucher's disease also is to be considered, but in our series not a single case was found The spleen alone was found to be definitely enlarged in more than 50 per cent of the cases of subacute bacterial endocarditis, leukemia, Hodgkin's disease and gumma The great frequency of splenic enlargement in subacute bacterial endocarditis is too little appreciated The presence of combined hepatic and splenic enlargement is valuable for differential diagnosis as shown in table 6 Combined enlargement is most often encountered in leukemia, subacute bacterial endocarditis and gummas of the liver

TABLE 9—*Death Rates per Hundred Thousand from Seven Principal Causes of Death in State of New York, Exclusive of New York City, from 1918 to 1926*

Cause of Death	1926	1925	1924	1923	1922	1921	1920	1919	1918
Heart disease	303	273	261	270	260	234	243	221	247
Cerebral hemorrhage	126	120	131	128	132	128	127	123	126
Cancer	121	121	120	117	115	114	109	106	104
Nephritis	121	118	112	111	111	110	117	116	128
Pneumonia	117	98	92	115	109	85	138	129	293
Accidents	86	89	88	90	82	76	78	76	88
Tuberculosis	85	89	91	95	95	99	112	126	145

Table 1 has been brought in only incidentally, as it illustrates some interesting facts, and the following comments, although obviously a digression, are of sufficient interest to warrant inclusion in this paper It will be noted that heading the list of causes of death is heart disease This is in accord with statistics as given in table 9 and the chart, general mortality statistics of the State of New York and of the United States Registration Area, respectively The malignant tumors in our series occupy second place, although in table 9 and the chart they occur in third place This is probably to be explained by the fact that, because tumors afford greater interest to clinicians, they come to autopsy more frequently Accidents hold third place in our series, and this figure is astounding The high mortality from this cause in our series can be explained by the fact that coroners' cases, which are so frequently cases of accidental death, are included in this study An important lesson to be drawn from this observation is that mortality statistics might be greatly lowered by proper prevention of these accidental deaths, since most of them are preventable

Pneumonia and tuberculosis appear lower on the list The figure for tuberculosis is probably a little low owing to the fact that many

patients die in distant sanatoriums, and this precluded postmortem studies by the department of pathology. The importance of acute and chronic alcoholism has already been referred to. There is one item in the list that needs special emphasis, and that is the relative infrequency of true nephritis or glomerulonephritis as a cause of death. It will be noted that deaths from heart disease were more than fifteen times as numerous as those from nephritis. This ratio is probably correct as judged from clinical experience, and the general statistics as shown in table 9 and the chart, where the death rate from nephritis is shown to be as high as from one half to one third of that from heart disease are unquestionably greatly exaggerated. This fact was emphasized by one of us in a previous paper,<sup>2</sup> where it was stated, "The frequency of nephritis is greatly exaggerated because many cases of cardiac decompensation associated with edema and albuminuria secondary to essential hypertension are being diagnosed as nephritis. A correction of this error would greatly lower the nephritic death rate and proportionately increase the death rate from heart disease." It is possible that the statistics on the general mortality from nephritis are four or five times the actual incidence, as no one can doubt the greater accuracy of statistics from postmortem studies as compared with those from the general mortality report. One more item in table 1 is worthy of note, and that is the very low incidence of deaths from typhoid fever. Owing to improved sanitary conditions especially in regard to water and milk supplies, typhoid fever now ranks among the minor causes of morbidity as well as of mortality.

#### REPORT OF CASES

CASE 1—M T S, aged 61, was seen in consultation on Nov 17, 1930. In July, 1930, he had had chills and fever, which lasted two days, and pain in the right side of the chest, the diagnosis was pneumonia. He spat blood several times. On August 9, he was discharged in good condition, but was readmitted on October 8 because of persistent cough and expectoration. A roentgenogram of the chest showed peribronchial infiltration. On October 13, the liver was found enlarged, it increased in size very rapidly and within a month reached to 4 cm below the umbilicus. On November 17, a diagnosis of primary carcinoma of the lung with metastases to the liver was made. The patient died on November 29. At autopsy, there were a massive tumor in the lower lobe of the right lung and a huge liver showing massive carcinomatous nodules, the organ weighing 6,150 Gm. The peripancreatic and perigastric lymph nodes were markedly infiltrated by the tumor. Histologic sections in the region of the portal veins showed carcinomatous infiltration of the wall of the vein with rupture into the blood stream. This finding explains the massive carcinomatosis of the liver, as well as the rapid enlargement.

CASE 2—B W J, a woman, aged 45, in March, 1930, began to have attacks diagnosed as disease of the gallbladder. Later pain developed in the left lower quadrant of the abdomen. On July 13, fever developed, with marked weakness,

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<sup>2</sup> Barron, Moses. Cardiac Decompensation and Its Treatment, Minnesota Med 12 487, 1929

nausea and progressive distention of the upper part of the abdomen. When seen on July 25, she presented an enormous liver extending 2 cm below the umbilicus, the liver had enlarged apparently in two weeks' time. The temperature was septic, with daily variations from 99 to 102.4 F and over. The blood showed about 50 per cent hemoglobin, leukocytes, 9,000 to 15,000, red blood cells, 3,300,000. The stools showed occult blood. Slight jaundice developed. A diagnosis of probable hepatic abscess or subdiaphragmatic abscess was made. Aspirations gave negative results. On August 5, laparotomy showed massive carcinomatosis of the liver with the primary growth probably in the sigmoid. In this case, the temperature misled the observers in arriving at a correct diagnosis.

CASE 3—A colored man, aged 33, was admitted to the General Hospital on Aug 30, 1930, with a history and physical findings of extensive pulmonary tuberculosis of two years' duration. The liver was found to be massively enlarged, extending to below the umbilicus. The urine showed 4 plus albumin, the blood, 38 per cent hemoglobin, 3,600,000 red blood cells and 34,200 white blood cells, the temperature was septic. The large liver puzzled the resident staff. A diagnosis of amyloidosis should have been easy in this case from the history and findings. At autopsy, the liver weighed 5,725 Gm, the spleen 550 Gm, and the kidneys 225 Gm. There was extensive amyloidosis in all these organs.

#### SUMMARY AND CONCLUSIONS

1 This article presents a critical analysis of the weights of livers and spleens in a series of 12,000 autopsies. Certain tropical splenomegalies and hepatomegalies were obviously not present. A few other splenomegalies, such as those resulting from Gaucher's disease, congenital hemolytic jaundice, polycythemia vera and Banti's disease, were also not encountered.

2 Enlarged livers and spleens—because of their accessibility to direct palpation—occupy a place of great importance in the diagnosis of certain conditions.

3 Ordinarily only a few diseases, carcinoma, melanoma, leukemia, amyloidosis and Hodgkin's disease, produce livers of a size that reaches to the umbilicus (about 4,000 Gm or over). A differential diagnosis between these conditions can usually be made. It is to be remembered that, in carcinoma, the spleen is seldom enlarged and very rarely is the site of the metastatic tumor.

4 A characteristic feature of some cases of metastatic carcinoma of the liver is the rapidity of the enlargement, which is explained by the rupture of the tumor cells into the portal vein.

5 Some cases of carcinoma of the liver present high septic temperatures.

6 In contrast to carcinoma, sarcoma does not produce enlargement of either liver or spleen.

7 Melanoma resembles carcinoma in producing massive hepatic enlargements.

8 Cirrhosis of the liver, contrary to the general belief, produces no pronounced hepatomegaly. Most cirrhotic livers in our series weighed at autopsy under 2,500 Gm. A moderate enlargement of both liver and spleen is common. The enlarged spleen often erroneously suggests Banti's disease.

9 Gummas of the liver (*hepar lobatum*) are very rare and produce no marked enlargements. Both liver and spleen are moderately enlarged in about one third of the cases.

10 Enlarged spleens are found in a great variety of conditions, but true splenomegalies occur principally in leukemias, Hodgkin's disease, amyloidosis, cirrhosis of the liver, subacute bacterial endocarditis and acute infections. One must consider also Gaucher's disease, congenital hemolytic jaundice, kala-azar and Banti's disease, although there is a tendency to exaggerate the frequency of the last named. In subacute bacterial endocarditis, the incidence of enlarged spleens is from 75 to 85 per cent, thus showing the great diagnostic importance of an enlarged spleen in this disease. The greatest cause of massive splenomegaly is leukemia.

11 Neither the spleen nor the liver shows any great enlargement in pernicious anemia.

12 Chronic amyloidosis should always be suspected when there is definite enlargement of the liver and the spleen in cases of chronic suppurative processes, especially when albuminuria is present.

13 A proper understanding of the principal causes of splenic and hepatic enlargement is of great assistance in establishing correct diagnoses in a variety of conditions producing enlargement of the liver and spleen.

# INFLUENCE ON CARBOHYDRATE METABOLISM OF EXPERIMENTALLY INDUCED HEPATIC CHANGES

## III CHLOROFORM POISONING

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Chloroform according to Mosiman and Whipple,<sup>1</sup> affects mainly the nuclei of hepatic cells. As described by Whipple and Sperry,<sup>2</sup> it produces hyaline necrosis which is of a strictly central distribution, widening out concentrically as the dose of the poison is increased. Chloroform can also produce moderate fatty degeneration in other organs. Occasionally, severe necrosis of the kidney tubules may follow the administration of chloroform, even leading to delayed death of the animal. Williamson and Mann,<sup>3</sup> Opie and Alford,<sup>4</sup> and Mosiman and Whipple all came to the conclusion that the liver is the only organ that is seriously injured by the administration of chloroform.

## METHOD

Chloroform was administered subcutaneously in single doses as a 33 per cent solution in oil to fourteen rabbits. Rabbit 739 was given 0.5 cc of chloroform per kilogram of body weight and rabbit 717, 0.75 cc, the rest received 1 cc per kilogram of body weight. The first rabbit was killed on the fifth day. The second animal survived. Of the other twelve rabbits, seven died from forty-eight to sixty hours later, and one died on the seventeenth day after poisoning. The remaining animals recovered. Blood sugar curves for these rabbits were obtained,

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From the Medizinische Universitätsklinik, Leipzig, Prof Dr Morawitz, Director

1 Mosiman, R E, and Whipple, G H. Chloroform Poisoning, Bull Johns Hopkins Hosp **23** 323 (Nov) 1912

2 Whipple, G H, and Sperry, J A. Chloroform Poisoning, Bull Johns Hopkins Hosp **20** 278, 1909

3 Williamson, C S, and Mann, F C. The Hepatic Factor in Chloroform and Phosphorus Poisoning, Am J Physiol **65** 267, 1923

4 Opie, E L, and Alford, L B. Diet and the Hepatic Lesions of Chloroform, Phosphorus or Alcohol, J Exper Med **21** 1, 1915

TABLE 1—*Blood Sugar Curves After the Modified Dextrose Tolerance Test and the Administration of Epinephrine in Rabbits Subjected to Chloroform Poisoning*

Number	Days Since Beginning of Poisoning	Blood Sugar After 5 Gm. of Dextrose in 100 Cc. of Water and 1 Unit of Insulin					Blood Sugar After 0.1 Mg. of Epinephrine				Average Blood Sugar for 3 Hr. After Dextrose, 3 Hr. and Initial Blood Sugar	Difference Between Average Blood Sugar for 2 Hr. After Dextrose, 3 Hr. and Initial Blood Sugar	Average Blood Sugar for 2 Hr. After Administration of Epinephrine and 3 Hr. After Epinephrine	Difference Between Average Blood Sugar for 2 Hr. After Administration of Epinephrine and 3 Hr. After Epinephrine
		Initial Blood Sugar	1/2 Hr	1 Hr	2 Hr	3 Hr	3 1/2 Hr	4 Hr	4 1/2 Hr	5 Hr				
717	Normal	112	155	162	119	83	112	151	191	166	129	+17	145	+62
	2	191	140	184	133	176	184	223	266	281	159	-32	225	+49
	4	108	148	176	169	151	148	135	119	159	151	+51	135	-16
	28	111	140	144	119	94	151	205	209	230	124	+13	182	+88
	2 days after second dose	191	187	180	148	74	126	97	94	101	162	-29	101	+27
	This rabbit had convulsions 1 hour after the beginning of the test and was unconscious with occasional convulsions from the second hour on, it died 30 minutes after completion of the test, liver examined													
	Normal	126	155	122	112	115	166	144	144	137	123	-3	145	+30
	3	115	112	103	72	90	104	112	140	153	94	-51	120	+30
	Animal killed 4 days later, liver examined													
	Normal	133	169	162	148	151	178	166	151	152	154	+21	163	+12
739	2	137	166	173	180	130	115	144	144	155	164	+27	137	+7
	4	137	126	115	140	119	169	209	184	173	128	-9	177	+57
	6	122	130	140	137	126	140	173	162	151	134	+12	154	+28
	9	122	158	169	137	137	171	169	137	148	148	+26	130	+13
	11	103	140	137	112	119	86	101	94	97	124	+16	98	-21
	13	140	158	126	115	101	163	130	130	142	121	-19	139	+38
	16	155	148	144	115	151	180	191	151	176	137	-18	172	+21
	18	130	144	126	101	97	148	138	158	137	117	-13	146	+49
	23	140	137	97	83	83	140	169	140	119	100	-40	138	+55
	27	104	90	65	47	43	115	140	119	101	63	-41	112	+69
801	32	151	176	155	148	137	173	166	166	151	153	+2	163	+26
	Second dose of chloroform													
	12 hours	130	155	158	162	151	176	169	158	140	176	+26	162	+11
	36 hours	115	148	140	140	148	86	112	119	130	141	+26	114	-34
	3 1/2 days	133	206	169	108	177	148	177	170	136	136	+3	155	+61
	6 1/2	97	155	151	58	50	112	122	115	130	99	+2	110	+60
	10 1/2	101	97	94	83	86	148	144	126	119	90	-11	130	+44
	The following day, animal was killed for glycogen analysis, liver examined													
	Normal	153	162	104	104	72	119	154	158	144	126	-23	135	+63
	12 hours	103	122	101	90	101	101	97	108	108	99	-9	101	+15
804	36 hours	108	122	126	94	119	108	115	130	119	113	+5	119	-3
	4 1/2 days	108	122	126	112	83	115	162	176	144	112	+1	142	+59
	6 1/2 days	97	119	104	122	108	133	130	112	137	113	+16	125	+17
	8 1/2 days, dextrose and water	113	151	144	137	122					137	+34		

11½	104	91	54	68	126	180	216	209	176	82	-22	189	+63
13½	108	97	86	83	76	119	141	133	141	107	-1	126	+50
15½	104	97	86	72	58		68	58		80	-21	63	+5
Rabbit was found dead next morning, liver examined													
S21	Normal	97	151	119	76								
24 hours	76	110	144	122	79	94	79	101	115	102	+5	94	+4
4 days, dextrose only	126	173	223	227	90					125	+49		
8	94	133	140	126	180					131	+75		
10	86	133	166	133	68					118	+34		
12	108	153	176	112	122					136	+50		
16	94	137		97	115					136	+28		
18	108	216	176	102	83					125	+31		
20	115	149	118	61	76					139	+31		
Experiment discontinued													
S24	Normal	151	187	158	115								
14 hours	133	184	202	202	104	148	169	126	112	139	-12	145	-21
36 hours	101	148	191	206	206	166	173	170	158	204	+56	173	-33
Animal found dead on the following morning													
S25	2½ days	140	184	187	180	162	191	194	191	176	+36	186	+24
10½ days	173	241	216	148	119	119	220	233	223	178	+5	201	+82
14½ days	97	140	140	83	79	137	169	158	119	107	+10	141	+62
16½ days	86	112	90	79	83	122	133	137	137	89	+3	126	+43
18½ days	79	79	76	54	61	86	137	130	119	67	-12	111	+50
21½ days	104	122	140	133	97	119	119	119	119	124	+20	116	+19
Animal given second dose of chloroform, died 2 days later													
S26	Normal	158	180	169	108	90							
14 hours	97	108	133	122	119	115	94	86	97	137	-20	101	-18
8½ days	72	97	133	22	32	76	97	86	72	68	+23	78	+46
10½ days	126	148	115	72	68	130	148	151	119	99	-1	131	+63
13½ days	104	122	130	86	90					105	+1		
15½ days	94	119	130	61	40					87	-7		
17½ days	97	148	194	104	61					129	+32		
21½ days	83	119	169	122	65					131	+48		
23½ days	94	104	137	94	58					100	+6		
Experiment discontinued													
S27	Normal	108	155	155	104	58							
26 hours	83	94	133	176	176					118	+10	112	-64
Animal died on the following day													
						119	108	94	79	144	+61		



TABLE 2—Significant Average Blood Sugar Figures After the Modified Dextrose Tolerance Test and After the Administration of Epinephrine in the Chloroform Poisoned Group \*

Hours After Poisoning	Number of Rabbits	Blood Sugar After 5 Gm. of Dextrose in 100 Cc. of Water and 1 Unit of Insulin					Blood Sugar After 0.1 Mg. of Epinephrine				
		Initial Blood Sugar	Peak of Curve	Difference Between Initial Blood Sugar and Peak	Average Blood Sugar for 3 Hr	Difference Between Average and Initial Blood Sugar	3 Hr Blood Sugar	Peak of Curve	Difference Between Peak and 3 Hr Blood Sugar	Average Blood Sugar After Epi- nephrine	Difference Between Average Blood Sugar for 2 Hr and 3 Hr
12	4	117 (150)	155 (175)	+38 (+25)	141 (139)	+24 (-11)	131 (101)	142	+11	127	- 4
12	2†						119 (112)	142 (166)	+23 (+61)	132 (149)	+13 (+37)
24	2	80 (103)	160 (153)	+80 (+50)	135 (110)	+55 (+ 7)	133 ( 69)	117	-16	103	-30
36	3	108 (147)	160 (173)	+52 (+26)	153 (140)	+45 (- 7)	159 (109)	144	-15	135	-24
36	2†						135 (112)	130 (166)	- 5 (+61)	117 (140)	-18 (-37)

\* In parentheses are given normal averages for the same rabbits

† Animals in which a postepinephrine curve was made before poisoning

beginning twelve hours after the injection of chloroform and continuing at intervals until the reestablishment of a normal sugar tolerance and a normal response to epinephrine<sup>5</sup> Data on these experiments are given in detail in table 1 In addition, average figures for the most important stages are shown in table 2

## RESULTS

*Acute Stage*—Four rabbits were tested twelve hours after receiving chloroform The blood sugar at the beginning of the experiment was markedly reduced in all animals The peak of the curve was at the one hour period in one rabbit and at the two hour period in two rabbits In all of the animals the three hour blood sugar was much higher than normal and also higher than the initial blood sugar Finally, the average blood sugar during the three hours was about the same as that taken before poisoning, but the increase over the initial blood sugar was much greater

The response to the administration of epinephrine was markedly lessened in two rabbits (801 and 804), as testified by a diminished increase of the average blood sugar In the remaining two animals (824 and 832) a distinct hypoglycemia was observed following the administration of epinephrine

All of the described abnormalities of sugar metabolism were most pronounced in the rabbit (824) that died two days after poisoning

Two different rabbits examined twenty-four hours after poisoning exhibited to an even greater extent all the effects of chloroform described for the twelve hour period In addition the average blood sugar after the administration of dextrose, water and insulin was also absolutely higher than that in the same animals when normal Our findings were again most marked in a fatal case (835)

The characteristic curves of acute chloroform poisoning were observed in three rabbits also thirty-six hours after the injection of chloroform The quantitatively most marked abnormalities occurred again in the rabbit that died during the following night

*The Stage of Recovery*—Forty-eight hours after the injection of chloroform, the sugar tolerance and the epinephrine response were still decreased However, as the first sign of recovery, the initial blood sugar was even higher than normal On the following two days marked fluctuations of the initial blood sugar were observed The limits of these fluctuations in the same recovering rabbit (the variation was as great as 94 mg ) were in excess not only of those found in successive tolerance curves of any one normal animal (up to 28 mg ), but of the extremes of all normal animals tested (up to 72 mg )

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5 For description of methods see our first paper Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes I Fasting and Administration of Thyroxine, Arch Int Med 50 46 (July) 1932

The peak of the blood sugar curve, the average blood sugar for the three hours and the three hour level also fluctuated considerably after the first two days, but the general tendency was toward normal. After a curve showing normal height and contour was reached, the recovering animals (five) went through a stage in which hypoglycemic curves were observed following the administration of dextrose, water and insulin. In the rabbit (739) that received the smallest dose of chloroform such a hypoglycemic curve was obtained on the fourth day after poisoning. In the other animals it appeared after between ten and eighteen days. An infection of the upper respiratory tract developed in the sixth surviving rabbit (821), and retarded the return of the animal's sugar tolerance to normal until the twentieth day after poisoning, when the investigation was terminated. Of the five rabbits which had shown hypoglycemia during the tolerance test one (739) was killed during this stage, another (804) died sixteen days after the poisoning, and the remaining three later again showed their normal sugar tolerance.

The blood sugar curve after the administration of epinephrine in recovering animals was also subject to wide variations, but normal figures were usually obtained about the fourth day after poisoning. No consistent changes in the blood sugar following injections of epinephrine were seen coincident with the hypoglycemic tolerance curves. The typical stages of chloroform poisoning are exemplified in the blood sugar curves shown in the accompanying chart.

The glycogen content of the liver in one rabbit examined at the time of this peculiar hypoglycemia was 1.2 per cent, whereas that of another animal after the administration of dextrose, water and insulin was 1.07 per cent.

#### ADDITIONAL EXPERIMENTS

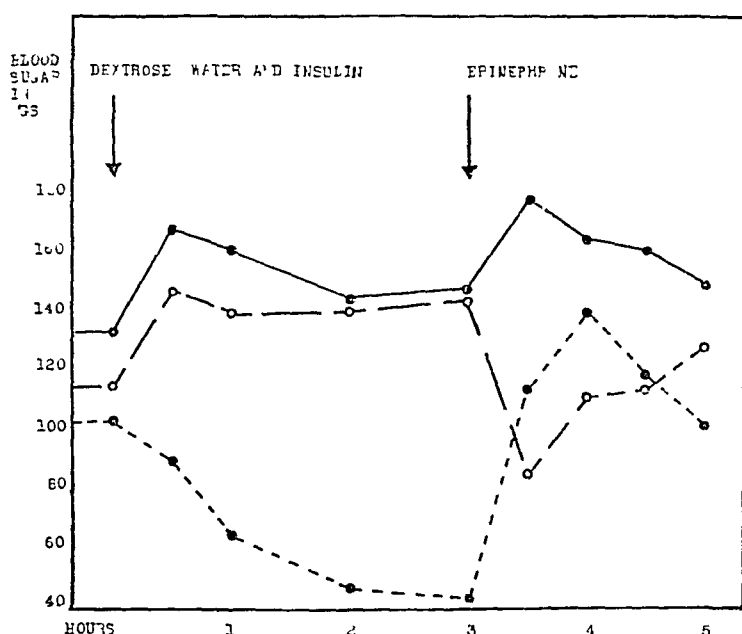
1 *Dextrose Tolerance in Chloroform Poisoning*—In order to investigate the possibility that some changes observed in the metabolism of carbohydrates under the conditions of the modified dextrose tolerance test might be due to damage of the pancreas, the same test was performed, with the omission of the insulin, in three rabbits at different stages of chloroform poisoning. As will be remembered, in three experiments on two normal rabbits<sup>6</sup> the increase of the average blood sugar over the initial level was approximately doubled when, instead of the standard conditions, dextrose only was given.

When dextrose alone was administered in the usual way to rabbit 821 four days after the poisoning, the increase in the average blood sugar during the three hours was approximately 50 per cent greater than the one observed twenty-four hours after the injection of chloroform, and a little more than double that seen eight days after this event following

<sup>6</sup> Descriptions of these experiments are given in the first article (footnote 5).

the tolerance tests with insulin. The same relative increase in the average blood sugar was seen in the second animal (804) after the test without insulin eight days following the administration of chloroform as compared to the modified tolerance test performed six and eleven days, respectively, after poisoning.

A test of dextrose tolerance without insulin was made on the twenty-fourth day on rabbit 801 during the stage when hypoglycemic curves after the administration of dextrose, water and insulin were observed. This showed that the average blood sugar decreased three times as much as in the usual experiment with insulin performed on the nineteenth day after chloroform had been given. Another experiment with insulin made during the same stage on the twenty-eighth day resulted in the



Typical blood sugar curves after the modified dextrose tolerance test and after the administration of epinephrine in a rabbit (801) at two stages of chloroform poisoning. The solid line represents a curve obtained in the normal state. The irregularly broken line shows the curve thirty-six hours after poisoning. The regularly broken line traces the curve twenty-seven days after administration of chloroform.

same degree of hypoglycemia as the one without insulin on the twenty-fourth day.

*2 Repeated Poisoning With Chloroform*—Three rabbits that survived the first episode of poisoning were given reinjections with the same dose of chloroform after exhibiting normal curves in our two tests, twenty-one, twenty-eight and thirty-two days, respectively, following the first dose. Two of these animals (717 and 825) died two days after the second injection of chloroform. The third rabbit (801) survived and went through the previously described cycle of changes

relative to sugar tolerance and response to epinephrine, except that the hypoglycemic stage of recovery appeared after ten instead of thirteen days. The animal was then killed for analysis of the liver.

#### PATHOLOGIC CHANGES

One rabbit that died two days after the first injection of chloroform and one that succumbed in the same length of time after a second injection were examined histologically. In the first (824) all hepatic cells except two or three rows around the portal spaces were necrotic and filled with fat. There was less fat near the portal spaces and in the centers of the necrotic areas. In the second case (717) necrosis involved about three fifths of each hepatic lobule around the central vein. The necrotic cells were full of fat droplets, and there were many wandering cells present.

The livers of three animals that had shown hypoglycemia after the modified dextrose tolerance test were studied histologically. The liver of the rabbit (739) that received the smallest dose of chloroform and was killed four and a half days afterward showed almost complete repair of what had evidently been a moderate injury, with occasional fat droplets.

The animal (804) that died sixteen days after poisoning had a liver that was practically completely restored to normal. Death in this case had nothing to do with the action of chloroform on the liver but was probably caused, as in one of the rabbits in the series of Opie and Alford,<sup>4</sup> by chloroform necrosis of the kidney tubules.

Finally the rabbit (801) that was killed eleven days after the second dose of chloroform had a liver presenting a normal microscopic picture with a little fat still scattered in spots.

#### COMMENT

In appraising the effects of a single large dose of chloroform to which about one half of the rabbits succumbed within from forty-eight to sixty hours with advanced central necrosis of the liver, one is struck by the similarity of the functional deficiencies to those produced by phosphorus poisoning, and this notwithstanding the anatomically different localization of lesions produced by these two poisons.

To begin with the initial blood sugar during the acute stage was markedly lowered in all rabbits. Twelve hours following the administration of chloroform, tolerance to dextrose, as judged by the curve during the first three hours after the test, was greatly diminished. This was indicated by retardation of the peak and prolongation of the period of hyperglycemia. Absolutely, the average blood sugar was about the same as in the normal rabbits, but the relative increase over the initial

level was much greater. At the twenty-four hour and thirty-six hour periods the same abnormalities of the curve were even more pronounced, and in addition the average blood sugar was also absolutely higher than it was previous to the poisoning.

The hyperglycemia due to epinephrine during the acute stage was greatly reduced in half of the animals and replaced by hypoglycemia in the other half.

Forty-eight hours after the administration of chloroform, as the first sign of recovery the initial blood sugar had risen. At later stages considerable fluctuations of the blood sugar level before the tolerance test were observed. Following the first two days the tolerance to dextrose of the rabbits also showed considerable variation, but the trend was toward normal. After normal tolerance was regained, as indicated by the shape of the curve and the average blood sugar, the recovering animals went through a stage of increased sugar utilization. Following this stage, the rabbits again exhibited their normal tolerance.

The response to epinephrine during recovery also varied within wide limits, but the normal degree of hyperglycemia was again found beginning about the fifth day after poisoning.

The glycogen contents of the livers of one rabbit investigated before and of one investigated after the modified dextrose tolerance test were found to be about equally low.

Practically everything discussed in connection with the significance of the changes produced by the administration of phosphorus applies to similar effects of chloroform poisoning. In addition, two features seen only after the administration of chloroform deserve special attention. The first is the protracted character of the hyperglycemia resulting in an unusually high blood sugar at the three hour period. This peculiarity raised anew the question of a possible injury to the pancreas.

In order to arrive at a decision on this point our usual tolerance test with omission of insulin was performed on three rabbits in different stages of chloroform poisoning. The expectation was that without exogenous insulin any considerable pancreatic damage would result in a greater increase of blood sugar, compared with the test that included insulin, than is the case under similar conditions in normal animals. Actually, in the experiments without insulin performed four and eight days after poisoning, the increase of the average blood sugar over the initial value was about 50 per cent greater than the preceding and a little over double that of the following tests with insulin. After allowing for some recovery of the animals during the intervals between tests, we found that the relative increase of the blood sugar was not in excess of that occurring in normal animals. The third tolerance test without insulin performed on the twenty-fourth day during the stage of

increased utilization of sugar showed a much lower curve than the preceding test with insulin which was done before this stage. The curve observed during the same stage after a test with insulin was identical with the one obtained without insulin. After these experiments, the participation of the pancreas in the reduction of the tolerance to sugar produced by chloroform, appears to be ruled out.

The second feature of chloroform poisoning requiring an explanation is the hypoglycemic curve following the test of dextrose tolerance (with or without insulin) which occurs at a certain stage of recovery as shown in the chart. These curves are doubtless an expression of increased utilization of sugar. The arguments in favor of this interpretation are numerous: in the first place, the fact that hypoglycemia begins within thirty minutes of the administration of dextrose, water and insulin, second, the appearance of hypoglycemic curves after sugar tolerance had once returned to normal, third, the fact that after a small dose of chloroform the characteristic low blood sugar was observed earlier, and, finally, the practically complete repair of the liver seen on microscopic examination at this stage, whether it occurred early after a light poisoning or late after a severe one. Observations of the same order, which were interpreted as indicating a period of hyperactivity of the newly formed hepatic cells, were reported by Whipple, Peightal and Clark<sup>7</sup> on an increased phenoltetrachlorophthalein output of the liver following repair after poisoning, and by Whipple and Hurwitz<sup>8</sup> in regard to fibrinogen.

It is certain that hyperactivity on the part of the regenerated hepatic parenchyma plays an important rôle in the increased utilization of sugar by the recovering rabbits. On the other hand, additional factors such as increased activity of the pancreas and of the tissues may also be at work. It seems probable that the compensatory function that the muscles and the pancreas exercise during the period of hepatic insufficiency may materially contribute to the observed hypoglycemia if this compensatory mechanism once established does not recede with the same rapidity as regeneration of the liver progresses. It is of interest that the glycogen content of the liver at this stage of recovery is still very low.

Three rabbits were given reinjections of the same dose of chloroform after recovery. Two of these animals (717 and 825) were dead forty-eight hours later. The third animal (801) lived and went through the

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7 Whipple, G. H., Peightal, T. C., and Clark, A. H. Tests for Hepatic Function and Disease Under Experimental Conditions, Phenoltetrachlorophthalein, *Bull. Johns Hopkins Hosp.* **24** 343 (Nov.) 1913.

8 Whipple, G. H., and Hurwitz, S. H. Fibrinogen of the Blood as Influenced by the Liver Necrosis of Chloroform Poisoning, *J. Exper. Med.* **13** 136, 1911.

stage of increased utilization of sugar earlier than the first time. While the number of experiments is too small for any conclusions, it may be pointed out that the results are in agreement with the opinion of Wells<sup>9</sup> that a previous injury to the liver predisposes to subsequent chloroform injuries. We have already had occasion to mention the finding by Davis and Whipple<sup>10</sup> of increased tolerance to chloroform in dogs immediately after recovery from the first dose. It is probable that in regard to the question of susceptibility of the liver to repeated doses of hepatic poisons the time that has elapsed since the administration of the preceding dose is an important factor. Our third case seems to indicate that when the action of the second dose of chloroform is not lethal, regeneration of the hepatic parenchyma takes place more promptly.

*The Modified Dextrose Tolerance Test in Man in the Light of Experimental Findings*—One of the main difficulties in reproducing in animals by a more or less acute toxic injury pathologic functional states found in certain diseases of the liver in man lies in the condensed nature of the obtained experimental findings. Functional stages that in patients last for weeks, months or years are limited in such animals to days or even hours and may easily be overlooked. Such an example is furnished by the difficulties of interpreting the blood sugar curves of rabbits that received a single large dose of phosphorus. When the results of the more chronic experiments are used as a key, the significance of these curves becomes apparent. If the attempt to reproduce in rabbits abnormalities in the regulation of sugar metabolism observed in human patients with hepatic disease has been at all successful, it is due to the fact that one of the cardinal functions of the liver is involved.

The majority of abnormal blood sugar curves following the modified dextrose tolerance test obtained on patients suffering from diseases of the liver show an initial hyperglycemia which often exceeds that of normal persons, and which before the end of the test drops to a marked hypoglycemia. The same features, namely curves showing reduced tolerance to dextrose followed by a fall in blood sugar, were most clearly observed in rabbits subjected to chronic phosphorus poisoning. In animals that had received large single doses of phosphorus and chloroform the same abnormalities could be identified, but because of the rapid succession of various stages of acute hepatic insufficiency their presence was not so striking.

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9 Wells, H. G. Chloroform Necrosis of the Liver, *Arch. Int. Med.* **1** 589 (July) 1908.

10 Davis, N. C., and Whipple, G. H. The Influence of Fasting and Various Diets on the Liver Injury Effected by Chloroform Anesthesia, *Arch. Int. Med.* **23** 612 (May) 1919.



The second type of abnormal curve seen in human cases which is characterized by a continuous fall of the blood sugar level finds its counterpart in the hypoglycemic curves obtained during the period of recovery from the effects of chloroform. Since curves of this kind were found largely in subacute yellow atrophy of the liver, alcoholism with suspected beginning cirrhosis<sup>11</sup> and late stages of catarrhal icterus, it seems logical to attribute to them the same significance, namely, temporary hyperactivity associated with regeneration of the hepatic parenchyma.

Occasionally, hypoglycemic blood sugar curves of the second type were encountered in advanced cases of cirrhosis with ascites, etc. In such patients the early hypoglycemia could hardly be taken for a sign of active regeneration of the liver, but probably is comparable to the very low blood sugar curves seen in two of our rabbits (803 and 833) a few hours before death.

#### SUMMARY

Rabbits receiving one large dose of chloroform were subjected at intervals to a modification of the dextrose tolerance test followed by an injection of epinephrine. Blood sugar curves following these procedures and determinations of the hepatic glycogen before and after the modified dextrose tolerance test were made.

In the acute stage of chloroform poisoning the blood sugar level was reduced in all animals. At the same time there was diminution of the tolerance to sugar, explained at least in part by lack of deposition of glycogen in the liver following the administration of dextrose, water and insulin. Hyperglycemia due to epinephrine was greatly reduced in some animals and replaced by hypoglycemia in others.

During the stage of recovery, the blood sugar level, the sugar tolerance and the response to epinephrine returned to normal. In addition these rabbits went through a period of increased utilization of dextrose.

It was established that pancreatic lesions played no important part in the observed abnormalities of carbohydrate metabolism.

An attempt was made to correlate the different blood sugar curves after the modified dextrose tolerance test in man with those of animals in various stages of hepatic insufficiency due to phosphorus and chloroform poisoning.

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<sup>11</sup> These patients were subjected to the test some time after the withdrawal of alcohol.

# TREATMENT OF LOBAR PNEUMONIA WITH CARBON DIOXIDE AND OXYGEN

REPORT OF TWENTY-SEVEN CASES

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Pneumonia has challenged man's therapeutic skill for centuries. Hippocrates and other members of the Greek school recognized the disease with its high mortality. Though progress has been made in the knowledge of the clinical features, morbid anatomy and bacteriology of the disease, the death rate remains essentially unchanged, and pneumonia is still one of the most widespread and fatal of all acute diseases.

Various forms of therapy have been heralded, each with claims of reduction in mortality. Chemotherapy, with the use of ethylhydrocupreine and of mercurochrome-220 soluble, has been tried. Vaccines have been used extensively. The greatest therapeutic triumph in pneumonia has been the development of specific immunizing serum. The work of Cole and Moore<sup>1</sup> in developing a specific serum for pneumococci of type I and that of Felton<sup>2</sup> in producing a concentrated serum for pneumococci of types I and II have added to the progress of medicine. One of the most recent forms of therapy suggested for pneumonia is the inhalation of carbon dioxide and oxygen. In this paper a brief review is made of the rationale of its use, and a report is given of twenty-seven patients treated by this method.

Carbon dioxide may be used to stimulate the respiratory center, as was demonstrated by Henderson and Haggard<sup>3</sup> in 1920. These authors used carbon dioxide to eliminate carbon monoxide from the blood of dogs after dangerous degrees of asphyxiation. A year later, in reporting their work on carbon monoxide asphyxia to the American

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Read before The Southern Interurban Clinical Club, March 19, 1932

From the Department of Medicine, Emory University Medical School, and the Emory Division of Grady Hospital

1 Cole, Rufus, and Moore, H F. The Production of Antipneumococcic Serum, *J Exper Med* **26** 537, 1917

2 Felton, L D. A Study of the Isolation and Concentration of the Specific Antibodies of Antipneumococcus Sera, *Boston M & S J* **190** 819, 1924

3 Henderson Yandell, and Haggard, H W. The Elimination of Carbon Monoxide from the Blood After a Dangerous Degree of Asphyxiation, and a Therapy for Accelerating the Elimination, *J Pharmacol & Exper Therap* **16** 11, 1920

Gas Association, Henderson and Haggard<sup>4</sup> stated that in a group of forty-three patients who survived gassing, the records of Bellevue Hospital show that in fourteen subsequent pneumonia developed and ten died. In not a single patient treated by the inhalation of carbon dioxide and oxygen did post-asphyxial pneumonia develop. They observed no harmful accessory features from the inhalation of carbon dioxide.

In 1929, Coryllos and Birnbaum,<sup>5</sup> on the basis of experiments on dogs, considered lobar pneumonia to be a pneumococcic lobar atelectasis. Through bronchoscopic investigations on dogs they observed that infection of the walls of the air tubes produces an excessive and sticky secretion which tends to shut off the portion of the lung to which it leads. As the air in the involved part becomes absorbed, atelectasis develops, secretions accumulate back of the occlusion and consolidation follows.

In 1929, Henderson and Haggard<sup>6</sup> advocated hyperventilation of the lungs as a prophylactic measure against pneumonia. They stated:

Hyperventilation of the lungs by deep breathing under inhalation of carbon dioxide in proper dilution has proved effective in the prevention of postoperative pneumonia. It is effective also in the prevention of the pneumonia that may follow carbon monoxide asphyxia in untreated cases.

In 1930, Lincoln Brown<sup>7</sup> made bronchoscopic observations on patients with postoperative atelectasis while they inhaled carbon dioxide. He stated:

Carbon dioxide inhalations when observed through the bronchoscope were seen to (a) increase the rate and depth of respiration, (b) produce violent movements in the tracheobronchial tree and alterations in the shape of the lumens of its branches, thereby tending to free adherent mucus, (c) induce a distinct blanching of the mucous membranes of the trachea and bronchi.

The first paper on the use of carbon dioxide and oxygen in the treatment of pneumonia was published by Henderson, Haggard, Coryllos, Birnbaum and Radloff,<sup>8</sup> in January, 1930. Their work was

4 Henderson, Yandell, and Haggard, H. W. The Treatment of Carbon Monoxide Asphyxia by Means of Oxygen and Carbon Dioxide Inhalation, Report I, Commission on Resuscitation from Carbon Monoxide Asphyxia to the American Gas Association, *J. A. M. A.* **79** 1137 (Sept. 30) 1922.

5 Coryllos, P. N., and Birnbaum, G. K. Lobar Pneumonia Considered as Pneumococcic Lobar Atelectasis of the Lung. Bronchoscopic Investigation, *Arch. Surg.* **18** 190 (Jan.) 1929.

6 Henderson, Yandell, and Haggard, H. W. Hyperventilation of the Lungs as a Prophylactic Measure for Pneumonia, *J. A. M. A.* **92** 434 (Feb. 9) 1929.

7 Brown, A. L. Bronchoscopic Observations in Postoperative Atelectasis. Action of Carbon Dioxide, *J. A. M. A.* **95** 100 (July 12) 1930.

8 Henderson, Yandell, Haggard, H. W., Coryllos, P. N., Birnbaum, G. L., and Radloff, E. M. The Treatment of Pneumonia by Inhalation of Carbon Dioxide. I. The Relief of Atelectasis, *Arch. Int. Med.* **45** 72 (Jan.) 1930.

confined to experiments on dogs. These observers produced experimentally an obstructive atelectasis in dogs and relieved the condition promptly by short periods of inhalation of carbon dioxide and oxygen. They placed their dogs in closed chambers containing approximately 7 per cent carbon dioxide and 93 per cent oxygen. The dogs inhaled this gaseous mixture for periods varying from thirty minutes to one hour. As a result of the experiments, these observers considered pneumonia to be an atelectatic condition and could produce it by insufflation of virulent cultures of pneumococci directly into the bronchi of dogs. They called this condition a pneumococcus atelectasis and considered it to be identical with clinical pneumonias. These dogs were likewise placed in closed chambers containing approximately 7 per cent carbon dioxide and 93 per cent oxygen. They remained for periods of from thirty minutes to twenty-four hours. The pneumonia seemed to clear in some of the dogs.

#### CLINICAL INVESTIGATIONS

In November, 1930, we began investigations of the treatment of patients with lobar pneumonia with inhalations of carbon dioxide and oxygen.

*Administration of Gas*—The real problem was to select apparatus suitable to administer the gas to human patients. A Miller inhaler anesthetic mask and rebreathing bag were selected. The mask is constructed with two sets of valves which can be adjusted so that the patient inhales gas from the rebreathing bag and exhales it into the atmosphere. The gas thus flows in one direction and its concentration in the bag remains constant throughout the inhalation.

The gas was purchased previously mixed and analyzed so that each cylinder contained a mixture of 5 per cent carbon dioxide and 95 per cent oxygen. The problem of dosage then arose, that is, how long to administer the gas and how often to repeat it. We tried to secure this information by observing the effects on four normal persons, who inhaled the gas for periods of ten minutes. Each subject had the same experience of feeling slightly faint at the end of the period but recovered quickly, with no ill after-effects. Kymographic tracings taken during the inhalations revealed that respiration was increased from two to three times in depth and slightly in rate. The determinations of the pulse rate and blood pressure varied but slightly.

With this information, it was decided that patients with pneumonia could probably inhale the gas for a period of ten minutes, and that it could probably be given twice a day. The hours of administration were set arbitrarily at 8 a. m. and 8 p. m. Fourteen patients were treated on this schedule. The dosage was then increased. The remaining thirteen patients received gas for a period of ten minutes at 8 a. m. and 8 p. m., and for two additional periods of five minutes each at 12 noon and 4 p. m.

*Selection of Patients*—The criterion for selecting patients was that they should be in an early stage of lobar pneumonia, which could be verified by the history, physical examination or roentgenologic examination. Patients were selected from the medical wards and were rejected if the illness exceeded three days. Otherwise,

no discrimination was made on a basis of probability of recovery. Only patients in the early stages of the disease were chosen, because by daily roentgenologic examination the spread of the pneumonic process in the involved lung could be determined. It is obvious that in late cases with complete consolidation this fact could not be determined.

*Routine of Procedure*—Patients admitted with early symptoms of lobar pneumonia were questioned carefully about the duration and nature of their illness. They were then examined to localize the pneumonia. The findings were checked by roentgenologic examination. If evidence of an early pneumonia could be determined, the patient was added to the series for treatment. The inhalations were supplemented by the usual nursing on the wards, an increase of the intake of fluid with dextrose, the use of codeine if needed for restlessness and an attempt to control distention by a daily saline enema. The sputum was typed, and blood cultures were taken. The physiologic effects of the gas on the pulse rate, respiratory rate and blood pressure were recorded before, during and after each inhalation. An occasional estimation of the number of white blood cells was made before, during and after inhalations. Determinations of the vital capacity were made on the last thirteen patients before and after each inhalation. Finally, the sensations of the patient, such as headache, dizziness, fatigue and pleural pain, were recorded with each inhalation of gas.

Except when very ill, the patients were carried to the x-ray room daily for examination.

#### REPORT OF SERIES

Our series consisted of twenty-seven patients. A summary of the case reports is given in the accompanying table.

There were twenty-two male and five female patients. The age limits varied between 14 and 46 years. The average duration of illness before admission to the hospital was two days.

The site of the pneumonia in the involved lung was as follows: right upper lobe, seven cases, right middle lobe, seven cases, right lower lobe, ten cases, left upper lobe, six cases, left lower lobe, ten cases. There was one case of pneumonia of the right hilus. The pneumonia spread to one or more lobes in nine patients of the series.

The gas was given on an average of five and one-half days. The shortest period of administration was three and one-half days; the longest ten and one-half days.

The disease ended by crisis in twenty-four patients, and by lysis in three.

Sputum was typed in each case, with the following results: type I, one case, type II, two cases, type III, four cases, type IV, eleven cases, mixed, two cases, undetermined, seven cases.

There were fifteen positive blood cultures. The pneumococcus was recovered in seven cases, the streptococcus in two cases, the staphylococcus in three cases and the diptheroid bacillus in three cases.

Determinations of the vital capacity served as a valuable guide as to the degree of consolidation and as an index of spread to other lobes.

# Summary of Case Reports

Patient	Age	Sex	Days Ill	Lobes Involved	Spread to Other Lobes	Days Gas Given	Day of Crisis	Type From Sputum	Blood Cultures	Sensations	Complications	Deaths
1	46	F	2	Right lower	None	6	6	I ysis	Pneumococcus Negative	Took gas well	Diabetes mellitus	
2	38	M	1	Left upper	None	5	3			Headache, pain in chest	None	
3	23	F	3	Left lower	Left upper	6	6			Took gas well	None	
4	16	M	2	Right middle	None	5	3			Headache, pain in chest	None	
5	18	M	2	Right upper	None	6	6			Took gas well	None	
6	16	M	1	Left lower	None	1	2			Headache, pain in chest	None	
7	26	M	2	Right middle	None	1	2			Took gas well	None	
8	35	M	2	Left upper	None	5	7			Headache, pain in chest	None	
9	45	M	2	Left upper and lower	None	8	7			Took gas well	None	
10	29	M	1	Right lower	None	5	4			Took gas well	None	
11	35	F	3	Left lower	None	7	5			Pain in chest	None	
12	19	M	2	Left lower	None	3 1/2	3			Fatigue	None	
13	15	M	2	Left lower	Left upper	3 1/2	2			Slight fatigue	None	
14	30	M	1 1/2	Right upper	Right upper, right middle, right lower	6 1/2	6			Headache	None	
15	17	M	1	Right lower	None	10 1/2	7			Headache, fatigue	Puerperal sepsis, miscarrage	
16	25	M	1	Right upper	None	5	6			Took gas well	Empyema	
17	33	M	3	Right upper	None	7 1/2	7			Took gas well	None	
18	25	M	3	Right lower	None	6	14			Took gas well	None	
19	20	M	3	Left upper and lower	None	8	11			Took gas well	None	
20	39	F	1	Right hilus	None	6 1/2	4			Took gas well	None	
21	16	F	2	Right middle	None	5	4			Took gas well	None	
22	18	F	2	Right upper	None	6	2			Took gas well	None	
23	21	M	3	Right upper	None	6 1/2	4			Took gas well	None	
24	14	M	2	Right upper	None	5	4			Took gas well	None	
25	19	M	2	Right lower	None	6	2			Took gas well	None	
26	30	M	1	Left lower	None	7	7			Took gas well	None	
27	30	M	1	Left lower	None	4	5			Took gas well	None	
28						6	2			Took gas well	None	
29						7	7			Took gas well	None	
30						6	6			Took gas well	None	
31						1	1			Took gas well	None	
32						7 1/2	7 1/2			Took gas well	None	
33						1 ysis	IV			Took gas well	None	
34										Took gas well	None	
35										Took gas well	None	
36										Took gas well	None	
37										Took gas well	None	
38										Took gas well	None	
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86										Took gas well	None	
87										Took gas well	None	
88										Took gas well	None	
89										Took gas well	None	
90										Took gas well	None	
91										Took gas well	None	
92										Took gas well	None	
93										Took gas well	None	
94										Took gas well	None	
95										Took gas well	None	
96										Took gas well	None	
97										Took gas well	None	
98										Took gas well	None	
99										Took gas well	None	
100										Took gas well	None	

There was no constant response of the white blood cells before, during or after inhalations. The number was increased at times, while at other times it was decreased during inhalations.

The most common sensation experienced while the patients were inhaling the gas was headache. Seven patients complained of moderate to severe headache. Pleural pain was experienced by nearly all of the patients at the beginning of each inhalation but was not severe enough to be a contraindication for its use. Four patients complained of severe pleural pain. The majority of patients experienced some fatigue during inhalations, and when this was severe the periods of administration were shortened, much to the comfort of the patient. One patient had severe cough as a result of inhaling the gas. Administration was stopped because in this patient subsequent empyema developed. Sixteen patients took the gas well and experienced considerable relief from symptoms through its use.

#### COMMENT

The results of our series are interesting, though not dramatic. The series is small. We were unable to run a control series of early cases, owing to an inability to get patients in the early stages of the disease. From Nov. 15, 1930, to April 21, 1931, 114 patients ill with lobar pneumonia were admitted to the medical wards. Of these, twenty-seven were selected as suitable for treatment with carbon dioxide and oxygen. In this group there were two deaths, constituting a mortality of 7.4 per cent. The remaining eighty-seven patients were in various stages of pneumonia. Some of the patients were in the early stage of the disease, while others were in the advanced stage. The latter group was heterogenic so far as treatment was concerned. There were six patients who died within twenty-four hours and nineteen patients who received vaccine therapy without our supervision. Deducting these twenty-five, there remain sixty-two patients who received supportive treatment only. In this group there were twenty-two deaths. The mortality rate for this group was 35.9 per cent. A comparison of the death rates in the two groups is not justified as the effects of carbon dioxide and oxygen were not tried on patients in the moderately advanced or advanced stages of the disease.

Our investigations indicate that with the dosage and apparatus used, early pneumonia could not be aborted. The earliest evidence of pneumonia in some x-ray pictures was an interlobar pleurisy. Even with inhalations, from partial to complete consolidation occurred. Other films showed a mottling that proceeded to various stages of consolidation. There was no marked difference in the films of either half of the series, although in the last thirteen cases in which the gas was administered four times daily, there was apparently less tendency for

consolidation to occur. In several of these patients the pneumonia seemed to be held essentially in its original stage.

The tendency to spread to other lobes occurred about equally in both groups of the series. There were four instances of spread in the first half of the series and five instances of spread in the latter half.

Empyema occurred twice in patients receiving two inhalations daily and once in patients receiving four inhalations daily.

There was one death in each group. The first death occurred in case 2, in which pneumonia was complicated by puerperal sepsis and streptococcus septicemia. The second death occurred in case 26, in which pneumonia was complicated by a terminal pericarditis.

In the series as a whole, there were no appreciable effects on the pulse rate and blood pressure taken before, during and after each inhalation. Slight increases or decreases occurred in each at times, but they were of minor variation. Respiration was usually doubled or trebled in depth and increased slightly in rate.

Hypertension was not a contraindication for the use of the gas, as was seen in case 14, in which the blood pressure was 165 systolic and 120 diastolic. Carbon dioxide and oxygen caused only minor variations in this patient's blood pressure, and he made an uneventful recovery.

The effect on cyanosis was difficult to determine as all the patients were Negroes.

The patients invariably stated that they could breathe deeper and more easily immediately after each inhalation. Pleural pain was no contraindication. The pain was usually increased at the beginning of each inhalation, but subsided, as a rule, during administration of the gas. In some patients, the pain was relieved for from one to three hours after administration. In others, the gas had a sedative effect and the patients wanted to sleep. In none of the patients were chest swaths used, the thorax being left free to expand fully with each inspiration.

#### SUMMARY

1 Twenty-seven patients suffering with early lobar pneumonia were treated with inhalations of 5 per cent carbon dioxide and 95 per cent oxygen. There were two deaths.

2 So far as we could determine, inhalation of carbon dioxide and oxygen in this concentration is accompanied by no harmful effects.

3 The dosage and method of administration should be investigated further before inhalation of these gases is advocated for practical use in the treatment of pneumonia.



# QUININE DERIVATIVES AND SPECIFIC IMMUNE SERUM IN THE TREATMENT OF PNEU- MOCOCCUS INFECTION

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AND

IOHANNES K MOEN, M D

MINNEAPOLIS

From the replies returned by twenty-five prominent German clinicians in response to questionnaires,<sup>1</sup> it is evident that specific treatment of lobar pneumonia with immune serum has not as yet been generally accepted. Even in this country, an inquiry revealed that many physicians still rely on quinine derivatives and do not employ specific immune serum in treating lobar pneumonia. In view of the reports of Cole,<sup>2</sup> Cecil and Sutcliffe,<sup>3</sup> Park, Bullowa and Rosenbluth,<sup>4</sup> and others, showing the beneficial effects of type I serum in treating type I infections in a large number of patients it seems unfortunate that quinine is still being used to the exclusion of specific serotherapy.

Quinine was introduced in the treatment of pneumonia about fifty years ago, chiefly by Jurgenson and Aufrecht. A new compound ethylhydrocupreine was popularized by Morgenroth and his associates in 1911. Ethylhydrocupreine is more pneumococcicidal than quinine in vitro even in the presence of serum, which ordinarily protects pneumococci against bactericides. The studies of Moore<sup>5</sup> and of Baldwin and Rhoades<sup>6</sup> corroborate the reports of the effectiveness of ethylhydrocupreine in vitro and their statements are used by commercial interests to promote the use of the drug in pneumonia. Clinical reports concerning the beneficial effects of optochin or quinine in the treatment of pneumo-

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From the Department of Medicine, University of Minnesota

1 Med Klin **25** 1771 and 1811, 1929, Deutsche med Wchnschr **56** 566, 1930

2 Cole Rufus Serum Treatment in Type I Lobar Pneumonia, J A M A **93** 741 (Sept 7) 1929

3 Cecil R L, and Sutcliffe, W D The Treatment of Lobar Pneumonia with Concentrated Antipneumococcus Serum J A M A **91** 2035 (Dec 29) 1928

4 Park, W H, Bullowa, J G M, and Rosenbluth, M B The Treatment of Lobar Pneumonia with Refined Specific Antibacterial Serum, J A M A **91** 1503 (Nov 17) 1928

5 Moore H F J Exper Med **22** 551, 1915

6 Baldwin H S and Rhoades, D R Hygienic Laboratory Bulletin 1925, p 69

nia are, for the most part, unconvincing. Baldwin<sup>7</sup> has since devoted his attention to specific serotherapy of the disease. Cross,<sup>8</sup> in a recent publication favoring the use of ethylhydrocupreine, stated that his impressions in regard to the efficacy of the drug were based chiefly on clinical and bedside impressions. Such criteria are, as a rule, too unreliable for use as scientific data. Convincing evidence can be obtained only from careful studies showing a shortening of the duration of the disease, a diminution or elimination of bacteremia and a reduction of the mortality, such as have been demonstrated in the use of specific serum. Furthermore, it is impossible to evaluate the results of most studies of patients treated with quinine derivatives since in practically none have attempts been made to classify pneumonia on an etiologic basis in regard to type of pneumococcus.

If one considers the replies of the German physicians who have used serotherapy and found it valueless, it is evident that none of them have given univalent serum in large doses, intravenously, according to the method prescribed by Avery, Chickering, Cole and Dochez.<sup>9</sup> Most of them used polyvalent immune serum and administered small doses intramuscularly. Only a few mentioned that efforts had been made to ascertain the type of pneumococcus beforehand. Professor Kiehl, practically the only one to recommend serum therapy, determined the type of pneumococcus in his cases and administered immune serum intravenously with encouraging results. Fourteen of the twenty-five physicians questioned, including Sahli, von Bergmann, Eppinger, Curschmann and Schittenhelm, stated that they used quinine or its derivatives solvochin, transpulmin, plasmochin and ethylhydrocupreine exclusively. Of these drugs, solvochin<sup>10</sup> and transpulmin<sup>11</sup> have been found unacceptable for inclusion in "New and Nonofficial Remedies" by the Council on Pharmacy and Chemistry of the American Medical Association. Several of the clinicians saw no reason to introduce serum therapy in the face of the satisfactory results obtained from quinine. Of the remaining eleven, some did not have enough experience with serotherapy to give an opinion as to its worth, one (F. Meyer) stated that he uses serum and optochin in combination, and one (Weinberg) was skeptical of both serum and quinine therapy.

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7 Baldwin, H. S. *M. Clin. North America* **12** 679, 1928.

8 Cross, F. B. *M. J. & Rec.* **116** 271 and 354, 1927.

9 Avery, O. T., Chickering, H. T., Cole, R. I., and Dochez, A. R. Monograph no. 7, Rockefeller Institute for Medical Research, 1917.

10 Council on Pharmacy and Chemistry. Solvochin Not Acceptable for N. N. R., *J. A. M. A.* **96** 1477 (May 2) 1931.

11 Council on Pharmacy and Chemistry. Quicamphol (Transpulmin) Not Acceptable for N. N. R., *J. A. M. A.* **93** 1471 (Nov. 9) 1929.

Because of the preponderance of opinion in favor of quinine in the treatment of pneumonia expressed by these German clinicians, and since quinine preparations are widely advertised as specific for lobar pneumonia, it was considered timely to retest the effects of quinine on controlled pneumococcus infection and to compare its effects with those of specific immune serum. For this purpose, the new satisfactory method of inducing pneumococcus infection developed by Goodner<sup>12</sup> was employed. This method affords, under experimental conditions, a symptom complex that is analogous in several respects to lobar pneumonia in man. The method also renders it possible to observe and to compare the effects of various methods of treatment.

"Dermal" pneumonia is produced in rabbits by injecting small amounts of pneumococcus culture intradermally. A local lesion of the skin develops after eight to twelve hours which, histologically, resembles the reaction found in the human pneumonic lung. In from twelve to twenty-four hours, shortly after the appearance of the skin lesion, bacteremia and high fever develop (see chart 1 *B*). In untreated animals that die, the organisms in the blood increase in number; in animals that recover, the blood stream may never be invaded, or if pneumococci are present, they disappear. In Goodner's series of fifty-six untreated rabbits, forty-eight died, a mortality of about 80 per cent. If, however, specific antipneumococcus serum is given early in the course of the disease in sufficiently large doses, the organisms disappear from the blood, the temperature drops, and the animal usually recovers.

#### EXPERIMENTAL METHODS

Strains of type I and type II pneumococci obtained from the Hospital of the Rockefeller Institute, through the kindness of Dr. Avery, were used. Healthy rabbits were inoculated intradermally in the shaved skin of the abdomen with 0.2 cc of a 1:1,000 dilution of an eighteen hour broth culture of pneumococci. Rectal temperatures were recorded at least twice daily thereafter, and blood cultures were made once or twice daily until the animal recovered or died. Blood cultures were made by obtaining, accurately, from 0.1 to 0.2 cc of blood from the marginal vein of the ear, mixing it with 15 cc of nutrient agar containing 0.5 cc of sterile blood, at 45 C, and pouring plates. In this manner, the number of colonies of pneumococci could be counted after twenty-four hours' incubation, permitting a quantitative estimation of the intensity of the bacteremia.

Two quinine preparations were tested, quinine hydrochloride and ethylhydrocupreine (optochin base, "New and Nonofficial Remedies"), since these are the substances most commonly used clinically. Quinine hydrochloride was dissolved in distilled water and administered intramuscularly and intravenously. The dose given intramuscularly approximated the tolerated dose of from 30 to 70 mg per kilogram, as given by Solis-Cohen, Kolmer and Heist<sup>13</sup>. As a rule, 50 mg per kilogram

12 Goodner, K. *J. Exper. Med.* **48** 413, 1928.

13 Solis-Cohen, S., Kolmer, J. A., and Heist, G. D. *J. Infect. Dis.* **20** 313, 1917.

of body weight was given within eight hours in divided doses. In one instance, a rabbit died shortly after the injection of 50 mg per kilogram, but in some animals, as much as 120 mg per kilogram was given in three doses of 40 mg each at four hour intervals without evidence of poisoning. Quinine hydrochloride was given intravenously in divided doses so as to inject 30 mg per kilogram within eight hours. The tolerated dose is stated to be from 20 to 30 mg, and the lethal dose 50 mg, per kilogram<sup>13</sup>

The water-insoluble ethylhydrocupreine was dissolved in olive oil. Two per cent solutions were used. The solution was injected subcutaneously so that 150 mg per kilogram was given in divided doses. One animal received 275 mg per kilogram in forty-eight hours. Ethylhydrocupreine in 2 per cent solution in olive oil was also injected directly into the stomach by means of a ureteral catheter. Rabbits received 400 mg of ethylhydrocupreine in two doses within four hours. To three animals, 200 mg was again given the following day, making a total of 600 mg. This amount is approximately one fourth of the total dose (2.4 Gm) recommended for human beings for a similar period of time (Cross<sup>8</sup>). The insolubility of ethylhydrocupreine in water and its low solubility in oil precluded intravenous or intramuscular therapy. Blood cultures were made before and after the commencement of treatment, in most cases twice daily.

A potent antipneumococcus (horse) serum was administered intravenously within the first few hours after the onset of fever. The dose recommended by Goodner was used—0.23 per cent of the body weight. In some cases, the dose was repeated once or twice the same day. Blood cultures and registrations of temperature were made as in the observations with drugs.

In most experiments, sets of four rabbits were studied, two animals were treated, and two served as controls.

## RESULTS

The strain of type I pneumococci used in these experiments proved to be exceptionally virulent for rabbits. All of the seventeen untreated control rabbits died. Death usually occurred on the first or second day after inoculation. Bacteremia was present in each case. The strain of type II pneumococci was less virulent, eight of eleven inoculated rabbits survived. Bacteremia did not occur in any.

*Effect of Quinine Therapy*—Although large doses of quinine hydrochloride and of ethylhydrocupreine were given early in the course of infection, all of the twenty-two rabbits thus treated succumbed to infection. Nine died one day after inoculation, eleven two days after and two three days after, which was similar to the behavior of the untreated controls. A typical experiment is illustrated in chart 1 A.

Although large doses of ethylhydrocupreine were given, bacteremia persisted unaffected, and the animal died in two days. In none of the experiments, except one, was there any evidence of diminution of fever or of prolongation of life as compared with the controls. In all animals infected with type I pneumococci bacteremia developed, and in none, except one, treated with quinine salts was there any evidence of effect on the bacteremia. In the one exception, the temperature dropped to normal,

and the bacteremia diminished from 1,000 to 10 colonies per cubic centimeter of blood following an intramuscular injection of 120 mg of quinine hydrochloride, which is double the usual tolerated dose. The bacteremia and fever both increased rapidly again, within a few hours, and the animal died on the third day. In many instances, the number of circulating organisms increased during the treatment until death occurred.

We were unable to demonstrate any appreciable effect of quinine salts on the course of pneumococcus infection in rabbits. No difference was noted in relation to the route of injection of the drugs, nor were any differences noted between the effects of quinine hydrochloride and those of ethylhydrocupreine. All of the twenty-two treated and seventeen untreated rabbits died.

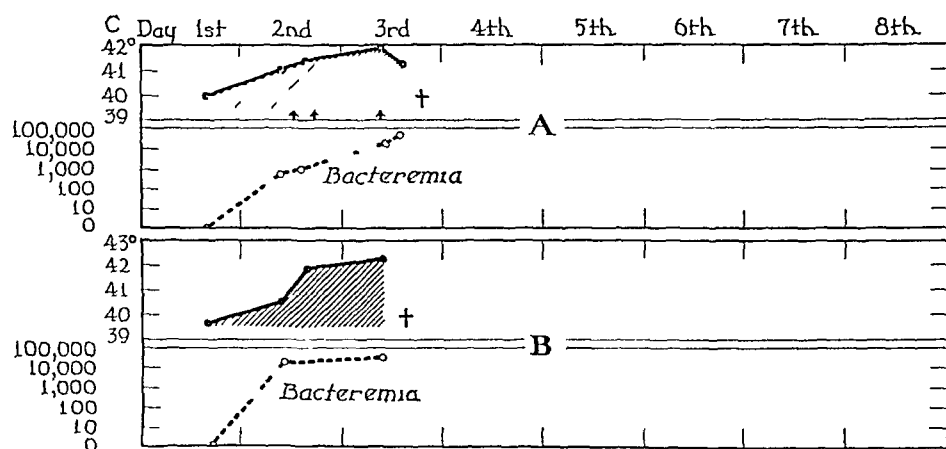


Chart 1—The temperature curve and the number of pneumococci per cubic centimeter of blood at various intervals in a rabbit (A) treated with ethylhydrocupreine, as indicated by the arrows, and in an untreated control rabbit (B)

In animals inoculated with type II pneumococci, ethylhydrocupreine was likewise without effect. A typical experiment is illustrated in chart 2 C. As shown in the chart, one rabbit (C) received two doses of 200 mg of ethylhydrocupreine base per kilogram, but died five days after inoculation. The control animal (D) recovered on the sixth day. In another experiment, four rabbits all recovered from infection on the fourth or the fifth day. The course of the infection in the two animals treated with quinine was no different from that in the two controls.

*Effect of Serotherapy*—Since the striking therapeutic effects of specific immune serum duplicated the results reported by Goodner, only a few animals were thus treated. Several experiments were performed, with sets of four rabbits each. In two experiments there were two treated and two control animals. All of the controls died. Of the four treated animals, two recovered. In one of the two treated animals that died, the temperature dropped to normal and the pneumococci in the

blood stream diminished in number from 50,000 to 1,000 per cubic centimeter after one injection of serum. The next day, however, fever again appeared, bacteremia increased, and the rabbit died. A second dose of serum on the second day failed to save the animal. It is possible that repetition of the treatment within a few hours after the first dose would have saved both animals. In another experiment, all four rabbits were treated with serum. In each, bacteremia greatly diminished or disappeared after the first injection. In two, about 10 colonies per cubic centimeter reappeared when the next blood culture was made, but disappeared after the second and third injections of serum. One rabbit

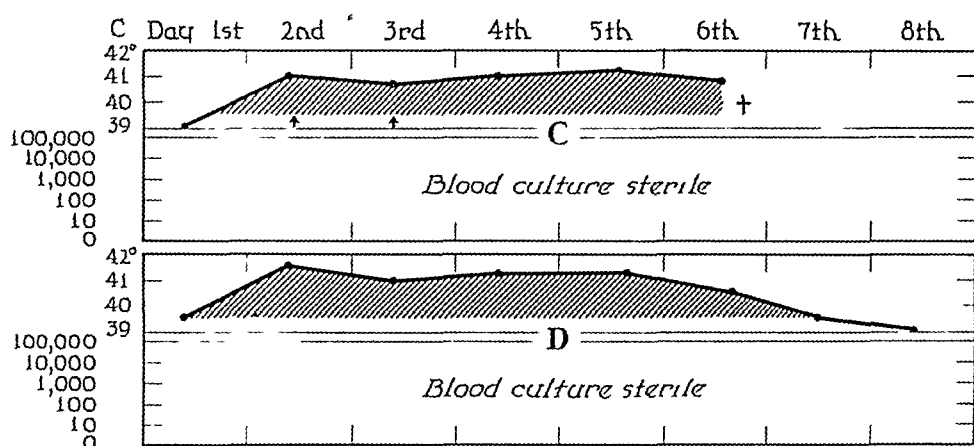


Chart 2—The absence of effect of ethylhydrocupreine in a rabbit (C) infected with type II pneumococci and treated with ethylhydrocupreine, as indicated by the arrows, compared with a similarly infected but untreated control rabbit (D)

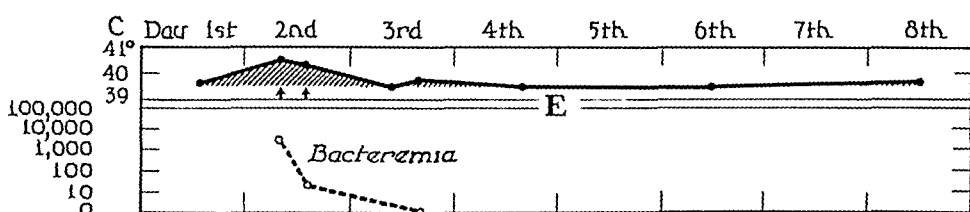


Chart 3—The therapeutic effect of type I serum administered to a rabbit (E) infected with type I pneumococci. The rabbit (1,800 Gm) received two intravenous injections of 4 cc each, as indicated by the arrows

recovered on the first day and one on the second day, in one, fever persisted for four days before recovery. The fourth rabbit apparently recovered, the temperature dropped to normal on the second day, and the blood culture became sterile, but on the third day it was found dead. Necropsy revealed pneumococcic pericarditis.

The striking beneficial effects of specific immune serum in most of the treated rabbits was demonstrated by the reduction of fever and the elimination of bacteremia. Of eight animals treated with immune serum, five recovered. The record of one of the rabbits successfully treated with specific immune serum is illustrated in chart 3 E.

## COMMENT

The results of the experiments leave no doubt as to the superiority of specific immune serum in the treatment of pneumococcus infection in rabbits. Quinine hydrochloride and ethylhydrocupreine, although pneumococcidal *in vitro*, appear to have no effect on the course of the infection, on the bacteremia or on the outcome as compared with the controls. All of the twenty-two rabbits treated with quinine derivatives and all of the seventeen untreated animals died in approximately the same length of time after inoculation with type I pneumococci. On the other hand, five of eight animals treated with specific immune serum recovered.

Quinine salts had no influence on the course of the milder infections due to type II pneumococci. Treated and control animals recovered in approximately the same length of time.

## CONCLUSIONS

Quinine hydrochloride administered intravenously or intramuscularly and ethylhydrocupreine administered subcutaneously and by mouth had no effect on the course of experimental pneumococcus infection in rabbits.

Specific immune serum, when given intravenously early in the course of infection in adequate doses, eliminates pneumococci from the blood stream, reduces the fever and causes recovery in most of the treated animals.

# RESUSCITATION OF THE STOPPED HEART BY INTRACARDIAL THERAPY

## II EXPERIMENTAL USE OF AN ARTIFICIAL PACEMAKER

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Cardiac standstill, regardless of the sequential development of the etiologic factors responsible for its occurrence, constitutes a clinical problem of no little magnitude so far as a favorable outcome in any individual case is predicated on the initiation of therapeutic measures leading to prompt restoration of the automatic activity of the heart. The more or less dramatic events attending cardiac arrest, whether the scene be laid in a well appointed hospital operating amphitheater, a doctor's consulting room or in less favorable circumstances, are always associated with ill defined attempts to do something to restore cardiac function. In the brief interval before complete surrender to death has taken place and before utter helplessness has seized those administering to the dying person, many random and badly executed procedures are invoked with the last minute hope of resuscitating the stopped heart.

In a previous communication<sup>1</sup> I attempted to review the methods currently employed in restoring normal cardiac activity. It was pointed out that when complete asystole of the heart occurs, a relative anoxemia of the myocardium soon develops, as this disturbed chemical balance progresses, the irritability factors of the heart muscle as a whole are markedly altered, so that the physiologic response to stimuli initiated outside of the normal pacemaker area at the sino-auricular node is enhanced. Any external mechanical stimulus when applied directly to the heart may result in an ectopic contraction, there is considerable experimental evidence to indicate that the first beat under such circumstances is always extrasystolic (fig 6).

In the early phase of the anoxemic period, the development of a single ectopic contraction may be, and usually is, sufficient to restore normal sinus rhythm. Medical literature is replete with instances of

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Published by permission of Grant No 21A from the Witkin Foundation

Report of the Special Committee on Intracardiac Therapy of the Witkin Foundation

1 Hyman, Albert S. Resuscitation of the Stopped Heart by Intracardiac Therapy, Arch Int Med **46** 553 (Oct) 1930



resuscitation by such mechanical stimulation of the stopped heart. Surgeons have massaged the heart when it has stopped beating during the course of an operation, squeezing, pinching or any other manipulation that directly develops a focal point of irritability from which an extrasystolic beat can arise permits the heart to return to its own automatic activity.

The past decade has seen another and a perhaps more direct measure introduced into clinical medicine. Intracardial injection therapy has, since 1921, received more and more attention as a procedure in resuscitating the stopped heart. Many instances of recovery after the intracardial injection of epinephrine have been recorded in the literature, up to 1930, my previous report showed that there were about 250 cases in which intracardial therapy in one form or another had been resorted to, with a favorable outcome in about 25 per cent. Many other substances in addition to epinephrine—twelve have been described—when injected during the early anoxic phase of the asystolic heart will cause extrasystolic contractions and in suitable cases a complete return to normal auriculoventricular rhythm.

The indications for such intracardial injection therapy are rather clearly defined. Meyer's<sup>2</sup> classification of cardiac arrest divided all such instances into two groups. First are those in which the patient has died as the result of constitutional or infectious disease processes. For these, no favorable outlook is to be anticipated as the heart is no longer normal, having been concomitantly altered by severe pathologic changes in other parts of the body. The second group of patients, comprising those who have died on the operating room table, the street or the battle field as the result of shock, pacemaker disturbance or an unstable vagal mechanism, may be resuscitated by intracardial therapy as these hearts are fundamentally normal and unaffected by such pathologic changes as those in the former group. In other words, intracardial injection should be a mode of therapy available for persons free from cardiovascular disease who have suffered sudden "death" from one of the aforementioned causes.

The success of such intracardial injection procedures, regardless of the substance used, although epinephrine is by far the most popular, is due entirely to the prick of the needle thrust into the heart. Here again, a focal point of irritability is generated in the heart muscle from which ectopic beats may be initiated. As already indicated, in the first phase of the anoxic period the extrasystole, regardless of its site of origin, is usually promptly followed by sinus rhythm. When, however, the anoxic period extends into its second phase and when the chemical changes in the various structures of the heart have become so altered

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<sup>2</sup> Meyer, C. *Jahrb. f. Kinderh.* **107** 76 (Sept.) 1924

that the electrodynamic factors are irreversibly disturbed, such a point of focal irritability may persist and continue to initiate stimuli for many other extrasystoles. Instead of one ectopic beat there will be a long series of rapidly developing extrasystoles which may approach paroxysmal tachycardia. When the ectopic focus has developed in the ventricles as the result of the intracardial injection therapy, paroxysmal ventricular tachycardia can be quickly followed by ventricular fibrillation and then by vascular collapse and death.

It was for this reason that we suggested that the intracardial injection be made into the right auricle, here the same phenomena may take place. Extrasystoles rapidly initiated may pass quickly into paroxysmal auricular tachycardia and then into auricular fibrillation. The difference in this instance is that while ventricular fibrillation is incompatible with life, auricular fibrillation is a well known and easily handled clinical entity. The rationale of intra-auricular puncture is thus based on physiologic principles and may offer a favorable outcome in cases in which cardiac arrest has occurred in an otherwise normally functioning system.

Since the publication of the original paper in 1930, there has apparently been a rather general acceptance of our conception of the procedure of intracardial injection. Reviews and comments both here<sup>3</sup> and abroad,<sup>4</sup> as well as the more recent textbooks on the heart (for example, those of East and Bain<sup>5</sup> and Paul D. White<sup>6</sup>), have all served to focus attention on the desirability of utilizing this type of resuscitation therapy when indicated. The preferential site of the injection has also been discussed by several authors, the unqualified adoption of intra-auricular puncture has been recommended by some,<sup>7</sup> while it has been held inadvisable by others.<sup>8</sup>

Opportunity for further investigation of the problem has been generously afforded through an additional grant from the Witkin Foundation, experimental studies on certain physiologic functions of the disturbed heart muscle during the various phases of anoxemia

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3 These reviews and comments were published in the following journals: *J. A. M. A.* **95** 1939 (Dec. 20) 1930; *Am. Heart J.* **6** 302 (Dec.) 1930; *Canad. M. A. J.* **24** 462 (March) 1931; *Practical Medicine Series: General Medicine*, p. 593, *General Surgery*, p. 24, *General Therapeutics*, p. 48, Chicago, Year Book Publishers, 1931.

4 A review appeared in *Lancet* (**2** 83 [Jan. 10] 1931) and also in the *Zentralblatt für innere Medizin* (**60** 544 [March 23] 1931).

5 East, C. F., and Bain, C. W. *Recent Advances in Cardiology*, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1931, p. 254.

6 White, Paul D. *Heart Disease*, New York, The Macmillan Company, 1931, p. 875.

7 Intra-Auricular Puncture, editorial, *J. A. M. A.* **96** 1875 (May 30) 1931.

8 Henderson, Y. Intracardiac Therapy, correspondence, *J. A. M. A.* **97** 124 (July 11) 1931.

resulting from cardiac arrest have been attempted, and several general conclusions have become permissible. The first of these is that the anoxemia which immediately takes place in the heart muscle with the onset of ventricular standstill reaches a relatively high acid concentration within a brief interval, many laboratory investigators have shown that the curve of  $p_H$  concentration rises rapidly in heart muscle when the normal circulatory mechanism is disturbed.

Further studies have demonstrated that as the curve of  $p_H$  concentration rises, the rate of electric conductivity is markedly enhanced, in the beginning the two curves run almost parallel, but after a certain well defined interval the curve of conductivity rises much slower than the curve of acid concentration. Regarded from another angle, it may be said that the threshold of conductivity is considerably lowered during the initial stages of myocardial anoxemia. The irritability factors of the heart are thus at first increased, but as the myocardium suffers prolonged oxygen-want and increasing acid overbalance, there is a breakdown of the normal electrodynamic factors, so that there is no coordinated fiber response and muscle contraction.

During the period of hyperirritability mechanical stimulation of any type sufficiently intense enough to reach the heart muscle fibers will be followed by contraction, this contraction will necessarily be of the extrasystolic type since the stimulus for the beat arises outside of the normal pacemaker. We have previously pointed out that the auricles are physiologically better prepared to receive such ectopic stimulation than the ventricles, and that the circulatory demands of the body may be maintained over long periods of time by extrasinus nodal rhythm.

While it is true that ordinarily a single prick of the needle may be enough to produce a point from which stimuli for myocardial contraction can arise, the success of this procedure depends on the stage of anoxemia through which the entire heart is passing at the time that the injection is attempted. During the initial stages of the resuscitation period the response to such stimulation is almost always positive, but as the middle and later stages of this period are approached and as the electrodynamic balance of the entire heart becomes more and more disturbed, a single prick of the needle may not be sufficiently powerful enough to dominate the complicated physiologic mechanisms that arise. Two or even three or more needle thrusts may be required, the disadvantages of this procedure are obvious. Henderson<sup>8</sup> has already commented on the injury to the heart likely to follow such multiple punctures.

Since the entire phenomenon of stimulus production as the result of the mechanical irritation of the needle prick is dependent on the development of differences in electric potential, it would seem that a

control of the latter factor might favorably affect the chances of myocardial contraction. Moreover, the needle prick under such conditions offers only a single stimulus for the contraction of the heart, in laboratory animals this feature can be readily demonstrated. In a guinea-pig heart for example, after cardiac arrest occurs and after the resuscitation period enters into its second phase the needle prick initiates only a single cardiac contraction.

If the electric difference of potential could be rhythmically developed during this period of cardiac standstill it would appear *a priori* that regular contractions of the heart would follow, and under such artificial stimulus production an automatic activity of the entire heart might be maintained. When such a stimulus center is produced in the auricles the factor leading to a normal cardiovascular response is to be anticipated, and with the return of a favorable peripheral circulation all the vital organs unless irreparably damaged would again take up their normal functions. With the restoration of coronary circulation and with the disappearance of the chemical imbalance the myocardium will again resume its normal activity with the taking up of its own automatic sinus nodal rhythm.

The problems engendered by electrical stimulation of the stopped heart are not new, as long ago as 1862, Walsh<sup>9</sup> discussed the possibilities of causing the heart to contract by faradic stimulation of the sympathetic nervous trunks. Since that time there have appeared no less than sixty-five papers in the medical literature of continental Europe and America all concerned with various methods of reactivating the heart by electrical devices. For most part, the workers in this field have been interested in the stimulation of the neuromuscular mechanism of the heart and in the papers written before 1910 the general opinion seems to have been that the heart was subservient to neurologic-electric control.

More recently several authors have attempted to reanimate the asystolic heart by passing electric currents of different types through the chest, both high and low frequency differences of potential have been used and many kinds of electrodes have been employed. Kingsley, for example has experimented with a diathermic current in which the focal electrode was oriented in the heart muscle, a Japanese worker, in a further development of this theory, believed that increasing the temperature of the heart tissues would enhance the possibility of the restoration of automatic cardiac activity, and in some rather brilliantly performed experiments showed this to be true in laboratory animals.

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<sup>9</sup> Walshe, W. H. A Practical Treatise on the Diseases of the Heart and Great Vessels, Philadelphia, Blanchard & Lea, 1862, p. 155.

In 1929, at the Medical Congress held in Sydney, Australia, Gould demonstrated an electric device for stimulating the heart, this apparatus consisted of a neutral plate and a positive needle electrode which was inserted into the heart. Gould reported the case of a baby who was resuscitated by such electrical stimulations of this organ.

Prior to this, in 1927, we developed an apparatus for rhythmically stimulating a heart-lung preparation during a study that was being made on experimentally produced extrasystolic arrhythmias<sup>10</sup>. This apparatus, based originally on the Fiertz-Kaufmann induction coil stimulator familiar in one form or another in all physiologic laboratories, was constructed with a rotary polyphasic interrupter which permitted a known faradic current to be applied directly to the heart muscle. In the course of the experimental work on this subject a special needle electrode was developed, as the ordinary procedures utilize the single point method of stimulation with a neutral electrode grounding the entire heart (Rothberger).

While the studies on intracardiac therapy were being carried out, it occurred to us in April, 1928, that resuscitation of the stopped heart might be secured by applying procedures previously employed only in laboratory animals, at this time the needle pick theory of reactivating the asystolic heart was just being investigated. The replacement of the clinically employed hollow injecting needle by a special needle electrode that would carry a suitable stimulating current to the heart muscle now became a matter for special investigation. Since such a procedure would be, in effect, the employment of an artificial pacemaker acting in many respects like that of the normal sinus nodal pacemaker, there immediately arose the problem of the type and strength of the electric stimulus to be used.

The electrophysical phases of the problem were found to be beyond the scope of our own laboratories, so that assistance was required from several workers in the electrophysical departments of New York University. With their help a suitable apparatus was devised, a description of which follows.

#### THE ARTIFICIAL PACEMAKER, ITS DESCRIPTION AND MODE OF OPERATION

In its final form the artificial pacemaker scarcely resembles the original cumbersome, complicated and unwieldy apparatus that was developed to carry out the theoretical demands imposed on it for restoration of function of the asystolic heart. These demands can be briefly enumerated as follows: (1) imitation of the normal sinus nodal impulse in difference of electric potential, speed of release, rate of

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<sup>10</sup> Hyman, A. S. The Experimental Production of Extrasystoles in the Human Heart, to be published.

discharge and regularity of rhythm, (2) discharge of this current in that part of the heart in which a nearly normal cardiac response would follow (3) maintenance of rhythmic discharge over a controllable period of time (4) freedom from the need of accessory and perishable materials and (5) instant availability for emergency conditions

Studies involving resistance phenomena in various types of tissue, refractory periods contractility curves and other stimulant physiologic functions of muscles were made, and certain constants were finally experimentally established. The source of the electric current proved to be one of the greatest problems. Realizing that the apparatus was to be used for emergency purposes it soon became evident that it must

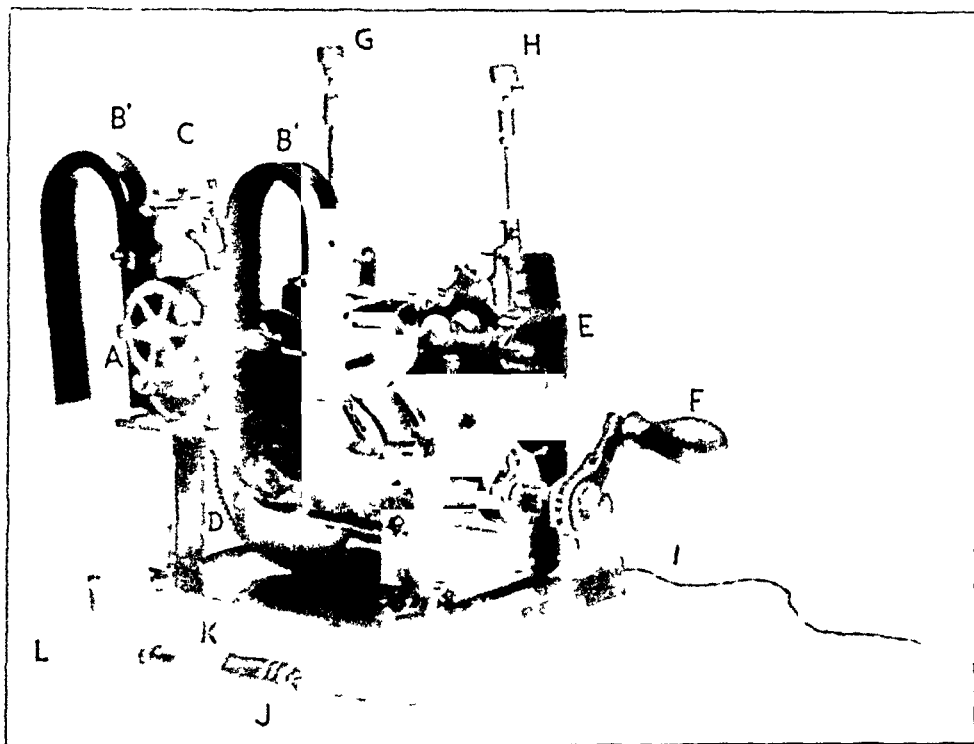


Fig. 1—The artificial pacemaker seen from the front. In figures 1 to 4 the following important features are to be noted: *A*, magnetogenerator, *B'* and *B''*, companion magnet pieces, *C*, neon lamps, *D*, spring motor, *E*, ballistic governor, *F*, handle, *G*, impulse control, *H*, speed control, *I*, flexible electric cord, *J*, insulated handle, *K*, handle switch, and *L*, electrode needle.

be prepared at all times for instantaneous action. For this reason, the use of batteries of any type was prohibited, the life period of commercial electric batteries, even when they are unused, is only about six months, so that unless new batteries were constantly being inserted, the machine might prove valueless when needed the most. Small generators were devised, only to be rejected because the type of current developed by them was not suitable for this work, moreover, the motive power required to spin these generators was too great to permit their use in a small portable apparatus.

Finally, a special form of magnetogenerator was constructed, with armature windings of sufficient size and number to develop the required stimulating current, an unusual type of built-up magnetic flux and the inclusion of a Tesla controlled break circuit on the armature brought into final fruition a very small and easily turned apparatus. A spring motor connected with appropriate gears and regulated by a ballistic governor was found to spin the generator for a period of six minutes with a remarkable constancy—a ratchet handle made possible rewinding of the motor without appreciably affecting either the speed or the power of the generator. In one experiment, the generator was kept in motion for four hours with no fluctuation in its output.

A rotary two-faced interrupter disk, geared at a definitely determined ratio to the generator armature, controlled the duration and speed of the electric current delivered to the outlet terminals. Three interrupter ratios were arbitrarily

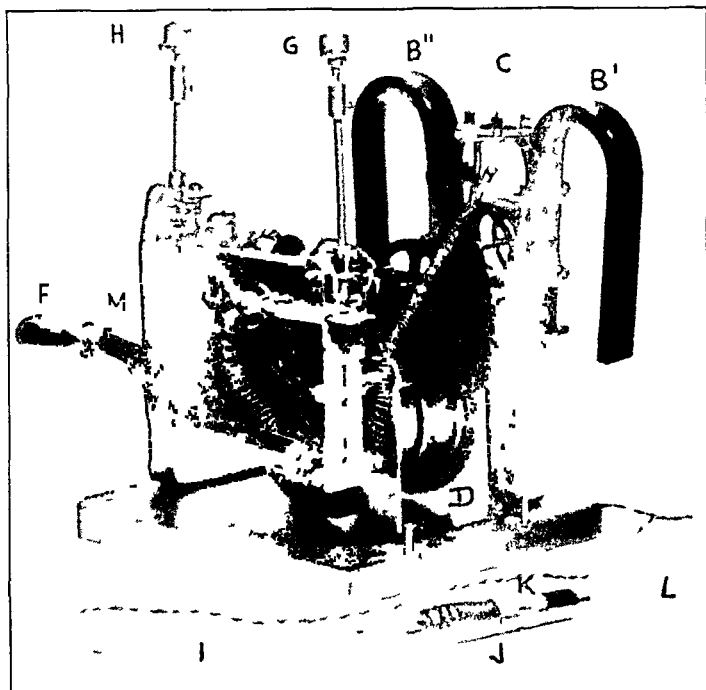


Fig 2—The artificial pacemaker seen from the back. The interrupter disk is shown at *M*.

determined, the lowest permitting 30 impulses per minute to be delivered, the next 60 impulses, and the highest 120 impulses. In order to demonstrate visually the production of the current and the rate at which it was being subdivided, special neon gas-filled bipolar lamps were utilized.<sup>11</sup> These lamps, consuming the lowest amperage of any known luminescent electric device, were activated on the negative side of the interrupter disk, and the brushes were so placed that when the current was not flowing to the outlet terminals, the lamps would glow. In other words, activation of the lamps alternated with release of the stimulating current, when the stimulating current was being delivered, the lamps were "dead."

Many highly technical and exceedingly complicated questions in pure electrophysics had to be solved before the apparatus could be successfully assembled,

<sup>11</sup> These were furnished by the Vapor Lamp Division of the General Electric Company which has cooperated in this particular phase of the work.

it is not within the scope of this paper to enter into any of these, save to point out that the capacity effect in the heart muscle itself had to be thoroughly studied and compensated for, as did the correction for the "lag" in muscle irritability.

Photographs of the apparatus are seen in figures 1 to 4. Figure 1 shows the front aspect of the artificial pacemaker. The principal parts of the equipment (as designated in the figures) are here described:

- I* magnetogenerator, note the Tesla control armature brushes
- B'* and *B''*, companion magnet pieces used in building up the required magnetic flux
- C* neon lamp cluster and current indicator
- D* spring motor
- E*, ballistic governor, the speed control of the spring motor
- F* handle for winding the spring motor with a ratchet arrangement to permit rewinding with the motor in action

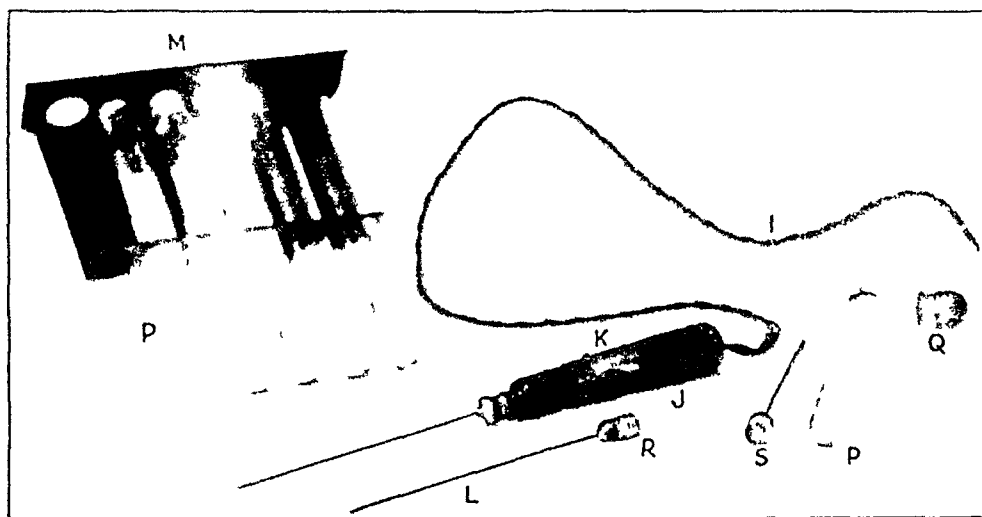


Fig. 3—Photograph showing details of needle (*L*) its electric connections (*R*, *S*), handle (*J*) and switch (*K*). The special tube holder (*M'*) and tube (*P*) with stopper (*Q*) are also seen.

*G*, impulse controller for regulating the position of the interrupter brushes and giving the three positions of 30, 60 and 120 impulses per minute.

*H*, speed control for the spring motor, an arrangement for starting and stopping the apparatus.

*I*, flexible electric wires for carrying the current.

*J*, insulated handle.

*K*, switch for controlling the current to the needle.

*L*, needle.

A posterior view of the apparatus is shown in figure 2. Here, in addition to the foregoing, is shown one face of the interrupter disk (*M*). In figure 3 is presented clearer detail in regard to the needles, the handle and the sterile containers for the needles. The needle (*L*) is a hollow steel shaft of no. 19 gage material through which runs a highly insulated wire that terminates at the same angle as the outside needle shaft. Electric connections are shown at *R*, the outside electrode, and *S*, the inside electrode. *M'* is a tube holder containing spaces



for six tubes in which the needles are sterilized by dried heat and kept until needed  $P$  represents such a tube, and  $Q$  is a specially prepared stopper selected for its impermeability

For clinical use the entire apparatus is enclosed in a sturdy well built carrying case, a photograph of which is seen in figure 4. The cover  $T$  is held firmly down by heavy trunk catches when not in use, when open, it carries a card  $O$  indicating directions. The tube carrier,  $M'$ , is seen in its compartment, the impulse regulator is seen at  $G$ , while the starter control is seen at  $H$ . The current terminal,  $N$ , to which is connected the flexible cord,  $I$ , is indicated in its relation to the handle and needle

The apparatus complete weighs 16 pounds (7.2 Kg.) because of the sturdy type of materials used to prevent damage in rough transportation

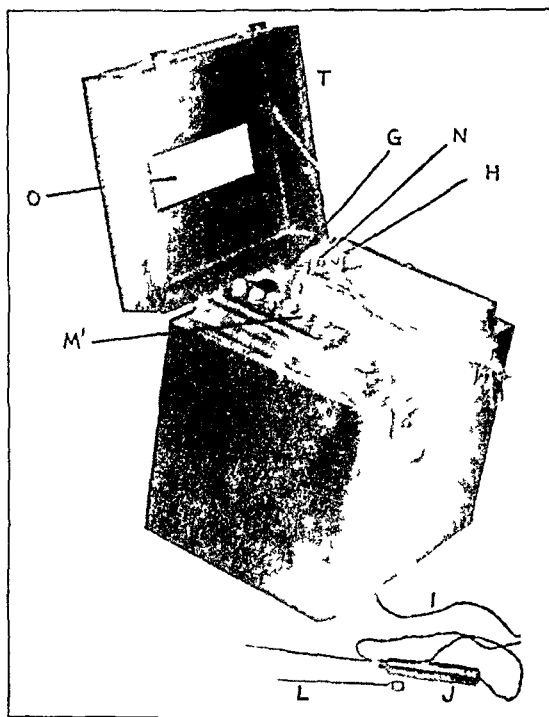


Fig 4—The artificial pacemaker in its carrying case

and employment under the most adverse conditions. A laboratory model built without such protective measures weighs but 8 pounds (3.6 Kg.), and it may be possible ultimately to reduce the size and weight of all models so that the apparatus can be conveniently carried in an ordinary hand bag.

#### EXPERIMENTS WITH THE ARTIFICIAL PACEMAKER

The successful development of the apparatus permitted its use in experimental work on laboratory animals. In November, 1929, a series of studies were made in order to determine the validity of the theories previously discussed in connection with restoration of function of the asystolic heart by controlled electric stimulus production. It soon

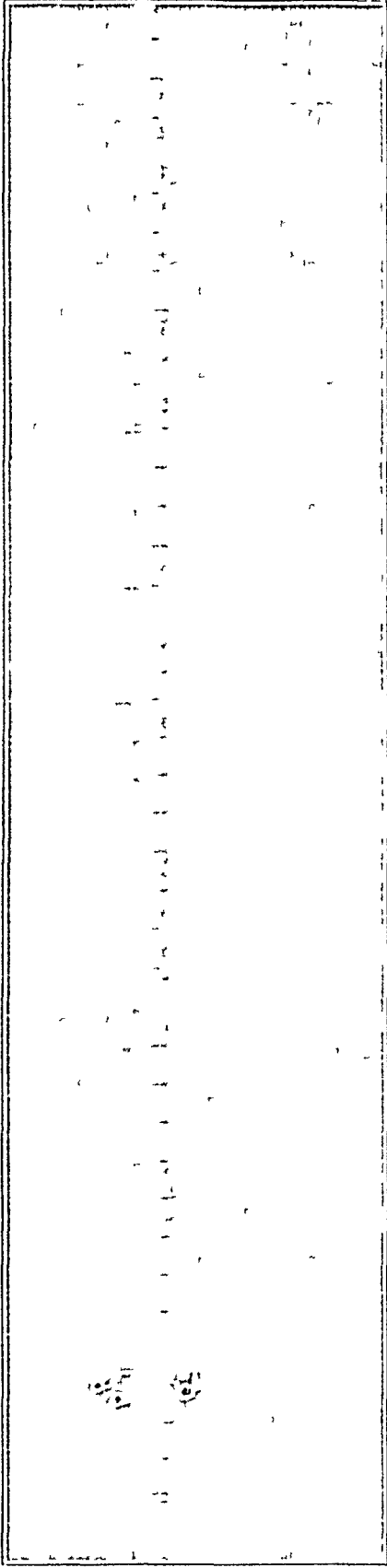


Fig 5—This electrocardiogram was taken before an experiment on the resuscitation of the stopped heart with the artificial pacemaker. A large healthy guinea-pig was used. There is a normal sinus rhythm with a rate of 300 beats per minute, the cardiac cycle is well defined. The P, Q-R-S and T waves are easily identified.

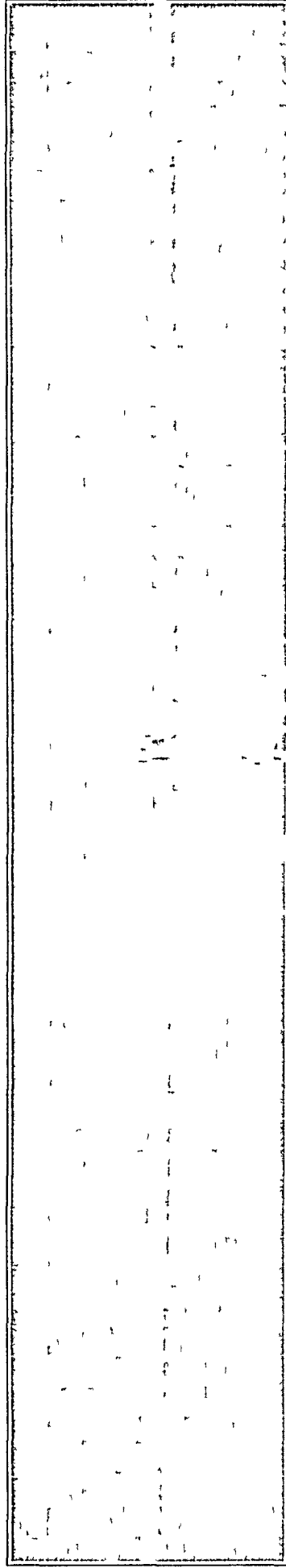


Fig 6—Immediately after the electrocardiographic tracings in figure 5 were taken, the guinea-pig was asphyxiated by a tracheal obstructor. Automatic respiratory movements ceased in one hundred and ten seconds, and seventy seconds later all signs of cardiac activity stopped. Exactly one hundred and twenty seconds after this the pacemaker needle was inserted into the right ventricle. This tracing, taken as lead II, shows complete cardiac arrest, the point marked by the arrow indicates insertion of the needle. It is accompanied by a ventricular extrasystole.

became evident that the type of needle used was of extreme importance and that the reasons for previous failures to resuscitate the heart by electric stimulation were due to the fact that *the entire heart was involved in the electric circuit*. In such cases the heart is unable to respond according to its normal mechanism, and the sequence of events in the cardiac cycle is considerably disturbed. When large differences of potential are used, the heart may go into fibrillation and all the phenomena found in electrocution are discovered<sup>12</sup>.

When, on the other hand, the electric stimulus enters the heart over a very small segment, this area becomes a focus from which the normal stimulus can pass through the heart over its customary pathways. From a theoretical point of view the closer the two electrodes carrying the stimulating current can be approximated, the nearer will this artificial focus approach that seen in the normal functioning organ. Of fundamental importance is the difference in the basic theories between the previous modes of electrically stimulating the heart and that concerned with artificial pacemaker methods. In the former, the electric current introduced into the heart is *the same current that is supposed to cause contraction of the heart muscle tissue*, whereas in the latter theory the introduced electric impulse serves no other purpose than to provide a controllable *irritable point from which a wave of excitation may arise normally and sweep over the heart along its accustomed pathways*.

In other words, the artificial pacemaker produces the same effect as that previously discussed in regard to the mechanical prick of an injecting needle, we have seen that in the latter condition the point of irritability that arises in the anoxemic myocardium generates its own excitation wave and that it is followed by certain well conditioned physiologic responses. The artificial pacemaker method proceeds one step further, while the needle prick alone gives only one opportunity for stimulus production, the rhythmically controlled artificial pacemaker permits many such stimuli to be applied over a period of time sufficiently long to enhance the probability of the renewal of automatic cardiac activity.

The practical use of the artificial pacemaker method of restoring the automatic activity of the stopped heart can, perhaps, be no better visualized than by the following experiments.

A large guinea-pig was "killed" by mechanical asphyxiation, a tracheal obstructor of the Porter type being used. When all respiratory movements had been stopped and no heart sounds could be determined, electrocardiographic tracings were made with the animal in the position of lead II (right foreleg and left hind leg). Figure 5 is the electrocardiogram taken prior to the experiment, the individual P, R and T waves are easily identified. Figure 6 was taken one hundred and twenty seconds after all evidences of cardiac activity had ceased, the

<sup>12</sup> Hooker, D. R. Am J Physiol **91** 305 (Dec.) 1929

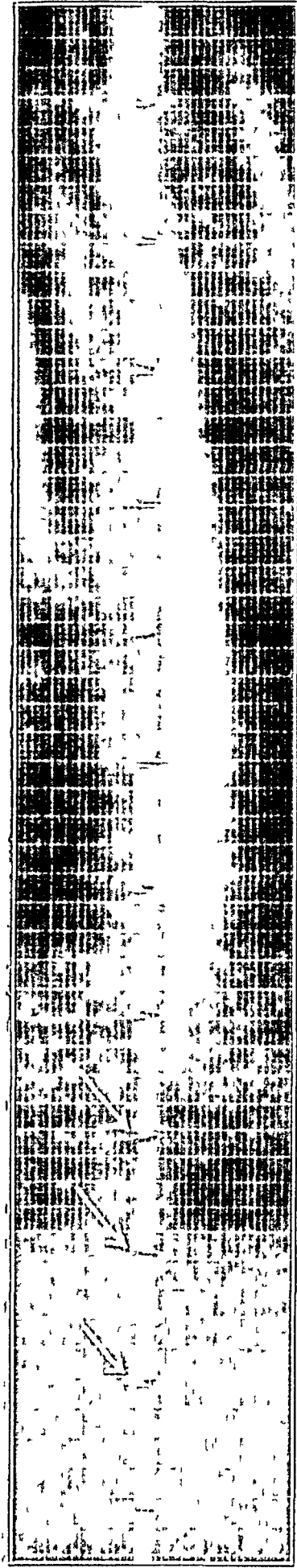


Fig 7—No further extrasystoles having developed within thirty seconds, the artificial pacemaker was started, a model BCM instrument was used. The rotor speed was set at 64 beats per minute. Note the periodic diphasic current occurring in the tracing.

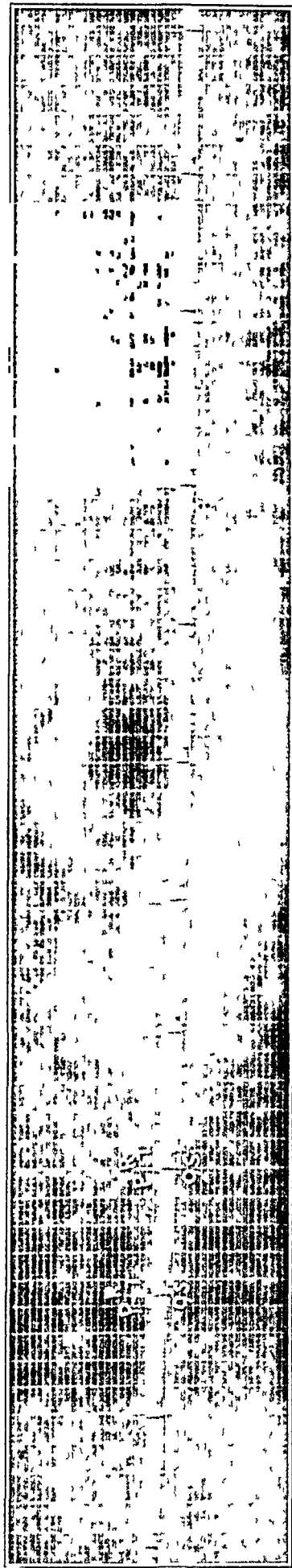


Fig 8—At the end of sixty seconds the artificial pacemaker was stopped and the needle withdrawn. Note the return of automatic cardiac activity with normal electrocardiographic waves, the P, Q-R-S and T waves being identical with those seen in figure 5. Of special interest is the rate, it is synchronous with the artificial pacemaker pulsations as seen in figure 7.

graph shows a straight line with certain extracardiac currents which 'cannot be removed without dampening the entire curve. These currents are constant and can be disregarded. At the point indicated by the arrow, a pacemaker needle was inserted high up in the right ventricle and an extrasystole promptly developed, but was not followed by any further signs of myocardial activity, the heart apparently being in the second phase of anoxemia.

After thirty seconds the artificial pacemaker current was started, and in figure 7 is shown the graphic tracings of the current effects in the anoxic heart muscle. The pulsations are readily seen to be regular at a rate of about 60 to 64 per minute. At the end of sixty seconds the pacemaker was stopped and the needle rapidly withdrawn, electrocardiographic tracings (fig 8) were taken and an especially interesting phenomenon was discovered. Normal sinus beats with readily recognized P, R and T waves were found to be developing at *exactly* the same rate as the previously developed artificial pacemaker ratio. This rhythm continued for about forty seconds, after which the normal sinus rate reestablished itself. In figure 9 is shown the return to a rate slightly faster than that seen before the experiment.

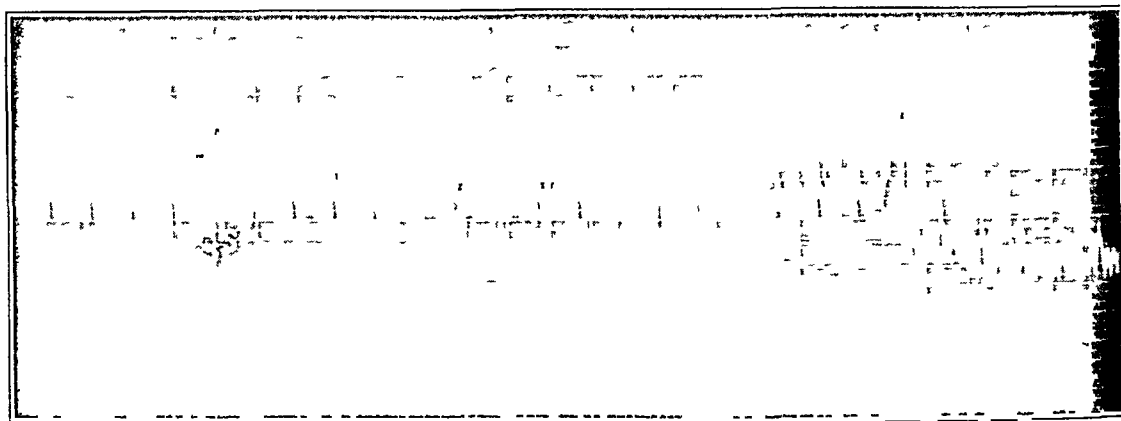


Fig 9—Return to normal sinus rhythm after forty seconds of restored cardiac activity, the rate is now slightly faster than that seen in figure 5 at the beginning of the experiment.

This experiment was repeated many times on other guinea-pigs, rabbits and one large dog, different modes of producing cardiac standstill being employed. It was soon found that whereas the current delivered by the artificial pacemaker had been calculated to meet the needs of the human heart, the stimulus produced in small animals was at times excessive in that widespread myocardial activity occurred much in the same fashion as that already discussed in connection with the older methods of resuscitating the stopped heart. For this reason, certain resistance units were added to the circuit when smaller animals were being used.

In figure 10 is shown an experiment carried on with a large guinea-pig when the pacemaker current was not dampened. The graphic records are interesting in confirming the theory of greater myocardial involvement when stronger currents are used. Figure 10 shows the record of the asystolic heart taken in lead II. Figure 10B demonstrates myocardial activity during the introduction of the

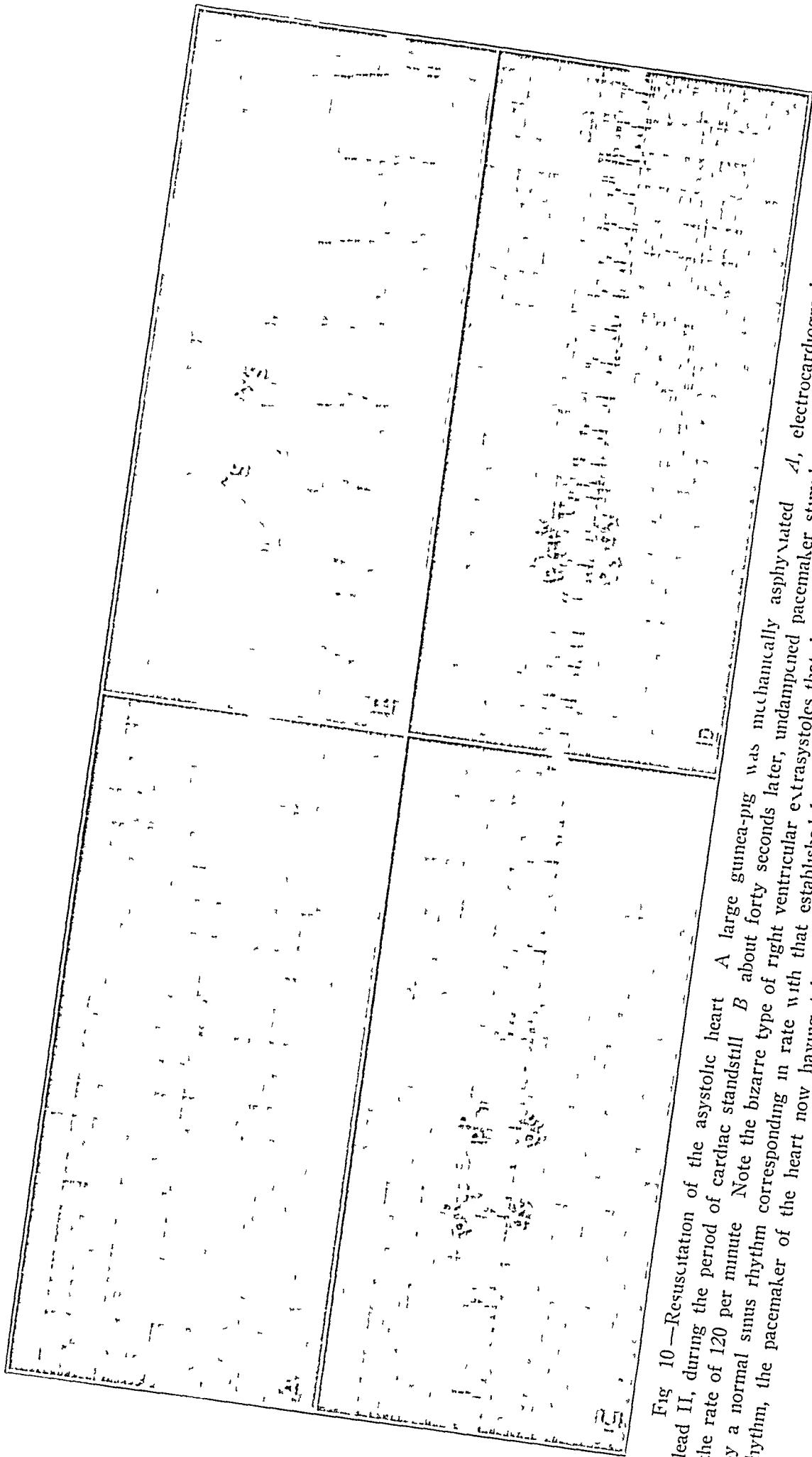


Fig 10—Resuscitation of the asystolic heart A large guinea-pig was mechanically asphyxiated A, electrocardiographic tracing taken in lead II, during the period of cardiac standstill B about forty seconds later, undamped pacemaker stimuli were released in the right ventricle at the rate of 120 per minute Note the bizarre type of right ventricular extrasystoles that developed C, removal of the pacemaker needle was followed by a normal sinus rhythm corresponding in rate with that established by the artificial pacemaker D restoration to regular normal sinus rate and rhythm, the pacemaker of the heart now having taken over control of the cardiac cycle

stimulating current, the complex takes the form of a bizarre right ventricular extrasystole, the pacemaker needle apparently being nearer the base of the right ventricle than in the right auricle where it was directed. In figure 10C is disclosed a regular rhythm with the same rate as that developed by the artificial pacemaker. This rhythm continued for about one minute, when there was a sudden return to regular sinus rhythm (fig 10D).

From a purely laboratory point of view many interesting problems arise which are worthy of further study, one of the most important of these is an inquiry into the factors responsible for the return of sinus rhythm at exactly the same rate as that produced experimentally by the artificial pacemaker. In the initial stage of the restoration mechanism, the renewal of automatic cardiac activity seems to start at the same rate as that of stimulus release by the artificial pacemaker. Apparently rhythmic changes develop in the myocardium as a result of this impulse release and the sinus node seizes on these alterations as the first step back to its own rhythmic rate. Unquestionably, the problem is more complicated than this simple theory would indicate, and many factors not here considered may be responsible for this transitional step. In discussing this feature with physiologists we have been accustomed to employ the simile of the normal pacemaker "following in the footsteps of the artificial pacemaker until the former had recovered its equilibrium and could enter upon its own initiatory phenomena."

Experimental evidence in support of the theory of increasing anoxemia resulting in the breakdown of electrodynamic factors is graphically demonstrated in the following study.

In this case a rabbit was anesthetized until cardiac standstill had taken place. Figure 11A shows electrocardiographic tracings in lead III (left foreleg and left hindleg) taken about ten minutes after the animal was pronounced dead. An undampened pacemaker current at 60 impulses a minute was introduced into the right ventricle, and figure 11B shows the type of right ventricular extrasystoles that developed as a result of this experiment. The artificial pacemaker was run for ten minutes, electrocardiograms being taken from time to time. Two features of interest are apparent, the first is the alternating fatigue phenomenon of Winterberg seen in figure 11C, where every other extrasystole is becoming smaller. The second is the attempt at automatic renewal of the pacemaker. Small P waves being seen at a rate of 160 per minute. They are apparently unable to initiate a ventricular response because of the greater stimulus introduced by the pacemaker current.

In contrast to this phenomenon is that seen in figure 12, when the pacemaker needle has been introduced into the left ventricle of the normally beating heart. In this experiment, a guinea-pig was etherized and an artificial pacemaker current at the rate of 60 impulses per minute was introduced. The graph shows the normal sinus rhythm of 300 beats per minute, interrupted 60 times a minute by the introduced stimulus current. Each stimulus is followed by a left ventricular extrasystole whenever it does not meet the refractory phase of the cardiac cycle.<sup>13</sup>

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13 Parsonnet, A. E., and Hyman, Albert S. Applied Electrocardiography, New York, The Macmillan Company, 1929, p. 90.

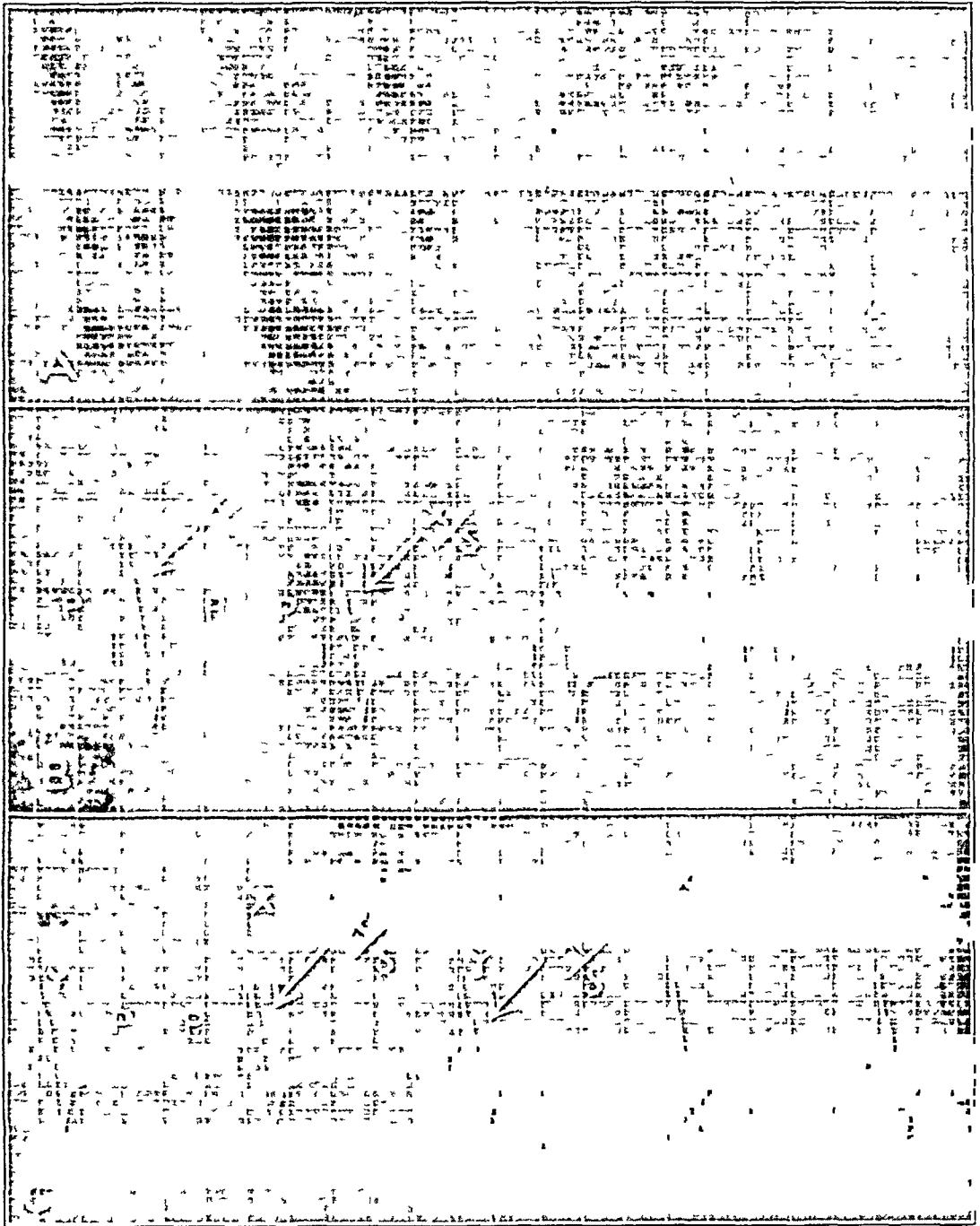


Fig 11—Experiment showing the effect of prolonged excitation from undamped artificial pacemaker stimuli. *A*, electrocardiographic tracing taken in lead III of the asystolic heart. *B*, undamped artificial pacemaker stimuli released in the right ventricle at the rate of 60 per minute. Note the development of auricular beats (P waves). *C*, tracings taken after ten minutes of artificial pacemaker control. Note the alternating fatigue phenomenon of Winterberg (*X*, large response, *Y*, small response).



The normal activity of the heart is apparently but slightly embarrassed by the artificial pacemaker current. The importance of this phase of the problem cannot be overemphasized, as the criticism has sometimes been made that the heart may actually be beating in certain patients who have been pronounced dead, in such persons it was thought that the introduction of the artificial pacemaker current might do damage to the cardiac mechanism. Apparently when the heart is contracting in response to its own stimulus production, the introduction of an irritable focus results in a response no wise different from that seen in the extrasystolic arrhythmias.

In the domain of pure scientific research, the artificial pacemaker opens avenues of approach to many problems in cardiovascular physiologic pathology, only two of these can be presented here. The suggestion was made by Dr. A. E. Paissonet that the artificial pacemaker might find a place in those cardiovascular disturbances which are clinically manifested by such gross irregularity of the circulation that death occurs. He had especially in mind those types of very rapid auricular fibrillation which are associated with low threshold values of the junctional and bundle tissues of the heart, in such instances the ventricular rate is also very rapid, reaching as high as from 180 to 220 irregular contractions per minute. The peripheral circulation is thus reduced to hazariously low levels, and stasis phenomena may develop.<sup>14</sup> With a pacemaker needle inserted in one or the other ventricle, it was thought that the ventricular rate might be controlled by this means when all other types of therapy had failed.

Paroxysmal tachycardia is another type of irregularity that not infrequently tests the skill of the clinician, responses to the ordinary modes of therapy are, as a rule, futile. When the focus of the new rhythm lies in the nodal area, vagal stimulation may interrupt the tachycardia and the return to a normal rate is prompt. More often, however, the ectopic focus lies in the ventricles, auricles or the Tawara nodal tissue, drug therapy in these cases is always disappointing. As the rhythm is extrasystolic in origin it should obey the Heiring law of maximal stimulation of muscle segments, the artificial pacemaker in such a case would release a stronger stimulus for contraction than the ectopic focus, and it would thus control the rhythm of the heart. Starting at a relatively high rate, say 160 or 180 impulses per minute, when control had been secured the normal rate could assert itself again. The employment of the artificial pacemaker in such disturbances of rhythm enters into other fields not immediately associated with the question of resuscitation of the stopped heart, it is mentioned here only to suggest profitable lines of inquiry made available by this type of apparatus.

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14 Hyman, Albert S. *Am J Pub Health* **19** 1103 (Oct.) 1929

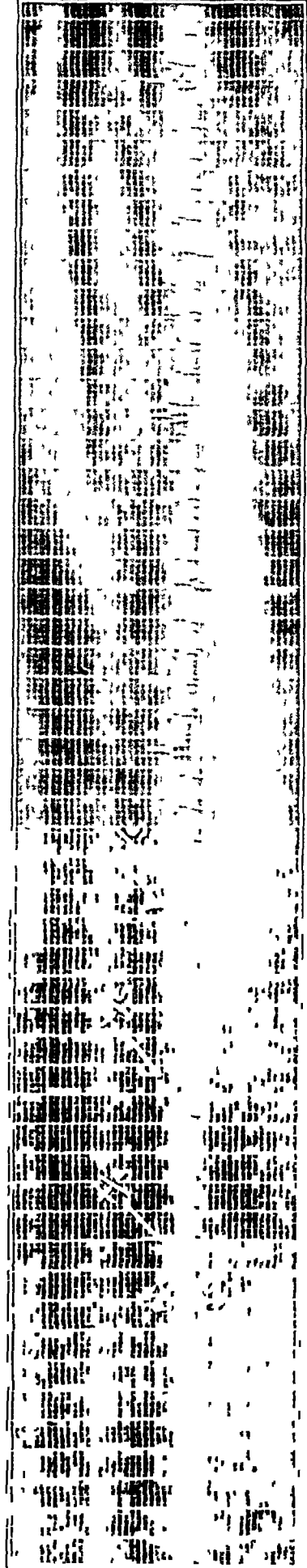


Fig 12—Experiment showing the effect of the artificial pacemaker stimulus in the normally beating heart. A guinea-pig was etherized, and electrocardiographic tracings were taken, the normal pacemaker is controlling the cardiac cycle with a rate of about 300 per minute. The artificial pacemaker is releasing its impulse at a rate of 60, each impulse is followed by a left ventricular extrasystole whenever the time relations are such as to permit ventricular response. Note that when the normal pacemaker and the artificial pacemaker are operating simultaneously the effect of the latter is the production of a regular extrasystolic arrhythmia.

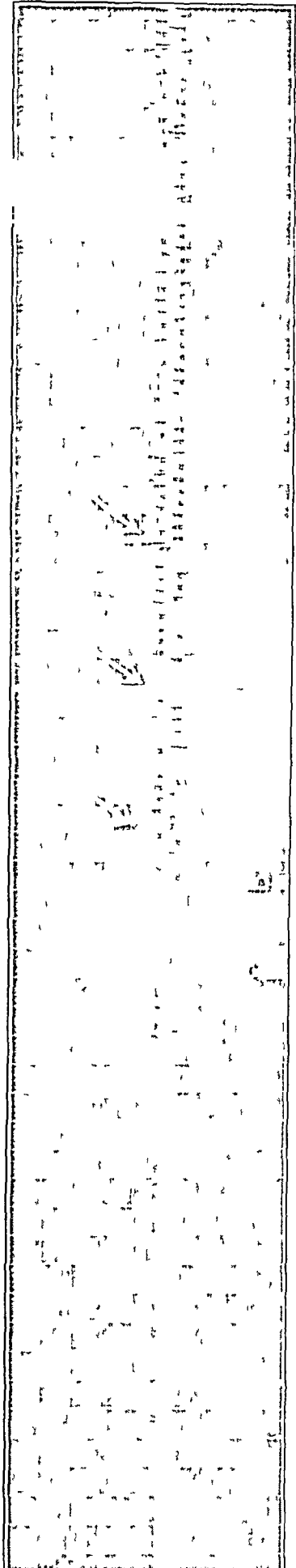


Fig 13—Electrocardiographic tracing (lead II) showing experimentally produced auricular flutter and fibrillation with ventricular control maintained by impulses from the artificial pacemaker. At point A, faradic stimulation of the auricles at a rate of about 900 per minute was begun while at point B the artificial pacemaker with an impulse release of 60 was started.

In figure 13 is shown a rabbit heart made asystolic by mechanical asphyxiation. At point *A*, the artificial pacemaker current at a rate of about 60 impulses per minute was introduced, and at point *B* a faradic stimulating current was applied to the exposed right auricle at a rate of about 900 impulses per minute. The graph shows ventricular rhythm maintained at a rate of 60, while the auricular rate is very rapid, at the rate of about 900. Figure 14 was taken four minutes later. The auricles are apparently not responding as rhythmically as at the beginning of the experiment. At point *C* this faradic current was stopped, but the pacemaker current was continued, the ventricles still responding regularly. These graphs are introduced merely to point out the wide field of applicability made possible by the artificial pacemaker.

#### THE CLINICAL USE OF THE ARTIFICIAL PACEMAKER

Sufficient evidence having been obtained from investigations on laboratory animals, the practical use of the theory and apparatus finally awaited trial in actual clinical fields. Having demonstrated that the insertion of a needle electrode carrying a rhythmic stimulus apparently caused no more harm to the normal heart than that of any other injecting needle and also having proved that such a rhythmically introduced current may carry on the rôle of the pacemaker of the heart until the normal pacemaker is able to reestablish itself, it was decided to use the method at first only on patients who had been pronounced dead and in whom all other methods of resuscitation had failed. The cooperation of clinicians interested in the problem was readily secured, once their objections to the possibility of the heart becoming "electrocuted" by this method was overcome.

The prejudice against intracardiac injection has long given way to the full acceptance of such therapy even before actual death has supervened. When the patient has "died," such objections as may still fill the mind of the medical attendant ordinarily disappear, the feeling being that no harm can come to the patient, and at the same time the possibility of resuscitation is always present. The use of the artificial pacemaker, radical as the procedure first appeared to some, soon gave way to a full acceptance of its use, and although the number of patients successfully treated by this method is still very small, a more or less widespread adoption of the method would unquestionably show the validity of the procedure.

It is hoped that with the publication of this work the method will come into greater general use and that a large series of figures may be obtained in order to give a true estimation of the value of the procedure. The histories of cases are not recorded here, but such satisfactory results have been obtained that the feeling has been that while the arti-

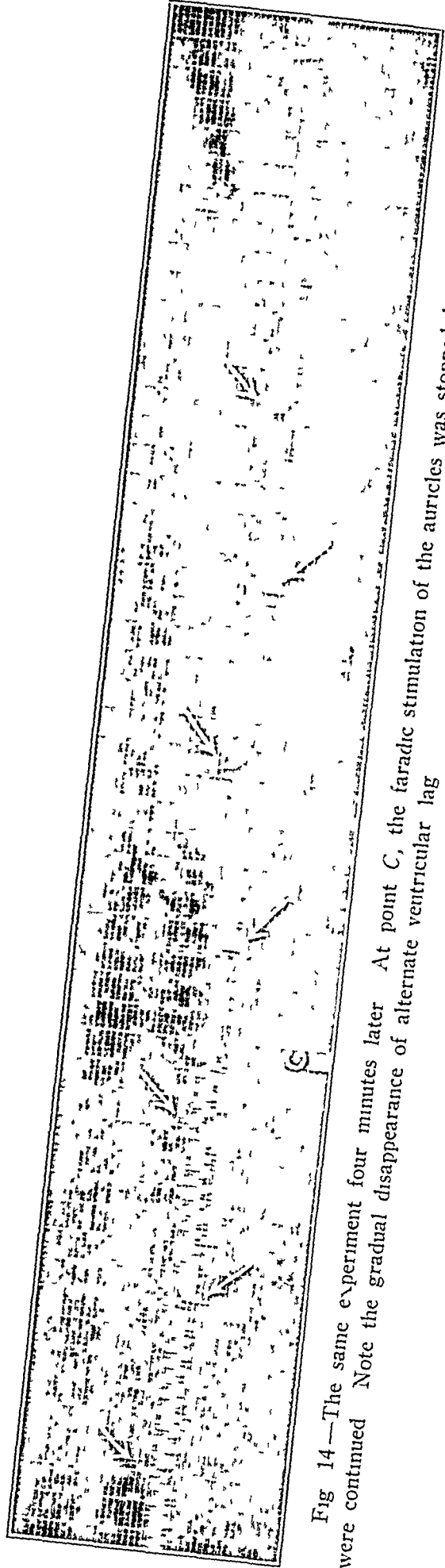


Fig 14—The same experiment four minutes later. At point C, the faradic stimulation of the auricles was stopped, but the pacemaker impulses were continued. Note the gradual disappearance of alternate ventricular lag

ficial pacemaker finds its greatest value in the resuscitation of the normal asystolic heart which has been stopped by the many causes previously enumerated, it also finds a place in the attempt to reestablish cardiac activity in those who have succumbed to death by other causes. The method is as yet too new to draw any hard and fast rules in regard to its uses, but its relative harmlessness in contrast to the favorable results to be anticipated recommends this type of resuscitation in all cases when the usual methods have proved futile. Even the saving of one life is sufficient to place the artificial pacemaker among those procedures now so eagerly seized when the emergency occurs.

#### SUMMARY

- 1 Stimulation of the stopped heart by electrical methods has previously failed because most investigators have attempted to reactivate the heart by neurogenic excitation.

- 2 When electric current has been applied directly to the heart, it has been done by placing the entire organ in the electric circuit, the result has been that the heart is unable to maintain its normal cycle. When strong currents have been used the factors discovered in electrocution are seen to be present.

- 3 In using a clinical needle through which is carried an electric impulse, and in having the two electrodes so close together that only a small pathway is concerned in the electric arc established by the heart muscle, an irritable point is produced.

- 4 This irritable point becomes the focus from which an excitation wave may spread over the heart muscle, the excitation wave developing and spreading according to normal physiologic conditions. The impulse released from the pacemaker needle differs in no way from that produced by the prick of any injecting needle except that in the latter instance only one stimulus is developed, while in the former any number can be delivered to the heart muscle.

- 5 An apparatus has been constructed which attempts to simulate the excitation wave developed by the normal sinus nodal pacemaker, it consists in a special current generated by a magneto which is activated by a spring motor, making it instantaneously available at any time, at any place and under all circumstances, as it is an independent electric unit. The current from this generator can be so regulated that the impulses are delivered to the needle point at a constant regular rate varying from 30 to 120 beats per minute.

- 6 The needles are carried in hermetically sealed tubes that have been sterilized. In the puncture procedure the same aseptic precautions must be observed as in any other sterile injecting manipulation. The

needle is inserted into an insulated handle which carries the terminals of the electric circuit from the generator. A convenient switch on the handle permits the current to be introduced into the needle at will.

7 Experimental animal studies have shown that the arrested heart is rapidly returned to automatic sinus activity after the response to the artificial pacemaker has restored some of the normal circulatory balance. Typical graphs are presented which show the electrocardiographic exposition of the events that take place in the heart when the artificial pacemaker is applied to the stopped heart.

8 The use of the artificial pacemaker in the normally beating heart is also shown and the relative harmlessness of the procedure is indicated, the result being the development of a regular extrasystolic arrhythmia. The artificial pacemaker impulse is followed by an ectopic beat from that area of the heart stimulated.

9 The question of utilizing the artificial pacemaker in certain gross irregularities of the heart is also discussed, but this field still requires considerable investigation before conclusions of any type can be considered.

10 In view of the possible advantageous results to be anticipated by the use of the artificial pacemaker in the arrested heart which does not respond to the usual methods of therapy the employment of this method is suggested. When patients have succumbed to disease processes, an attempt can be made to renew automatic cardiac activity by the use of the artificial pacemaker without in any way jeopardizing their condition.

11 When correctly used, the artificial pacemaker may prove to be of inestimable value in the restoration of those patients now succumbing to cardiac arrest, employed together with other established life-saving procedures it may well be included in every physician's armamentarium against the final struggle with death.

# FIBROMYOMA OF THE UTERUS, CARDIAC FAILURE, ANEMIA AND EDEMA

REPORT OF A CASE

H BRANDMAN, M D

CHICAGO

The fact that heart disease is associated with fibromyoma of the uterus is well known. The discussions of this association introduced by Hoffmeir<sup>1</sup> and continued by some of the early authors—Leopold,<sup>2</sup> Fehling,<sup>3</sup> Brosin,<sup>4</sup> Hennig,<sup>5</sup> Landau,<sup>2</sup> Kessler,<sup>6</sup> Wilson,<sup>7</sup> Doran,<sup>8</sup> Chavanez<sup>9</sup> and others—still continues. The more extensive and thorough work of later investigators—Boldt,<sup>10</sup> Healy,<sup>11</sup> Garkisch,<sup>12</sup> Strassmann and Lehmann,<sup>13</sup> Kelly and Cullen<sup>14</sup> and Janaki<sup>15</sup>—points to a frequency of simultaneous occurrence of the two conditions ranging from 20 to 40 per cent. Such a high figure does not seem to apply to carcinoma or

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1 Hoffmeir Ueber Erkrankungen der Circulationsorgane bei Unterleibsgeschwulsten, *Ztschr f Geburtsh u Gynak* **11** 366, 1885

2 Cited by Albrecht, H, in Halban and Seitz *Biologie und Pathologie des Weibes*, Berlin, Urban & Schwarzenberg, 1928, vol 4, p 415

3 Fehling Beitrage zur operativen Behandlung der Uterus Myome, *Zentralbl f Gynak* **18** 276, 1887

4 Brosin *Zentralbl f Gynak* **18** 96, 1887

5 Hennig, C Die Beweise fur den Wechselverkehr zwischen Herz und Gebarmutter, *Ztschr f Geburtsh u Gynak* **29** 131, 1894

6 Kessler, cited in *Am J Obst & Gynec* **46** 417 (Sept) 1902

7 Wilson, T The Cardiopathy of Uterine Fibromyoma, *J Obst & Gynec Brit Emp* **6** 107 (Aug) 1904

8 Doran, A Fibroids and Heart Disease, *J Obst & Gynec Brit Emp* **3** 13 (Jan) 1903

9 Cited by Cumiston, C G *Cardiac Disease and Uterine Fibromata*, New York State J Med **82** 893, 1905

10 Boldt, H J *Uterine Myofibromata and Visceral Degeneration*, New York State J Med **82** 887 (Oct) 1905

11 Healy, W P *Fibromyoma Uteri*, New York State J Med **97** 922 (May 3) 1913

12 Garkisch, A *Klinische und anatomische Beitrage zur Lehre von Uterus Myom*, Berlin, S Karger, 1910, p 9

13 Strassmann and Lehmann *Zur Pathologie der Myomerkrankungen*, *Ztschr f Geburtsh u Gynak* **38** 111, 1898

14 Kelly, H A, and Cullen, T S *Myomata of the Uterus*, Philadelphia, W B Saunders Company, 1909, p 451

15 Janaki, J *Herz Veranderungen bei Myom*, *Zentralbl f Gynak* **83** 2589, 1922

other diseases of the uterus or its appendages. This statistical concomitance has warranted the belief on the part of some gynecologists and internists that the new growth can specifically or uniquely injure the heart. Hoffmeir,<sup>1</sup> Biosin,<sup>4</sup> Strassmann and Lehmann,<sup>13</sup> von Lingen,<sup>16</sup> Hennig,<sup>5</sup> von Muller,<sup>17</sup> and others stated this opinion. On the other hand, some authors have denied this relationship. Severe critics of the hypothesis that fibromyoma is a specific danger to the heart are Winter,<sup>18</sup> McGlinn,<sup>19</sup> Martin,<sup>20</sup> Wilson,<sup>7</sup> Romberg,<sup>21</sup> Krehl,<sup>2</sup> von Jaschke,<sup>22</sup> and Walthard.<sup>23</sup> Winter was the first clinician and McGlinn the first pathologist to emphasize sharply the lack of critical judgment of some authors and the incomplete and inadequate study of patients supposedly having "Myom-Heiz." The former, also, called attention to the fact that such studies should represent the joint efforts and responsibilities of various specialists and not rest entirely on the shoulders of the gynecologist.

Some clinicians—Fleck,<sup>24</sup> Neu,<sup>25</sup> Herz,<sup>26</sup> Mahler,<sup>27</sup> Strumpell,<sup>2</sup> Aschner,<sup>2</sup> Freund,<sup>2</sup> and Romberg,<sup>21</sup>—conceived the new growth to be a focus or part of a group of phenomena relating to the disturbance of the endocrine glands. It was thought, for example, that the fibromyoma acted on the heart as does the thyroid gland in thyrotoxicosis, or that it was a passive or active agent in a general disease more manifested

16 von Lingen E. Ueber die Beziehungen zwischen Uterus Fibrom und Herz, Ztschr f Geburtsh u Gynak **66** 654, 1904

17 von Muller F. Die Bedeutung des Blutdrucks fur den praktischen Arzt, Munchen med Wchnschr **70** 1 (Jan 5) 1923

18 Winter, G W. Myom und Herz, Ztschr f Geburtsh u Gynak **87** 225, 1924

19 McGlinn, J A. Fibroid Tumors of the Uterus, Surg, Gynec & Obst **18** 180 (Feb) 1914, The Heart in Fibroid Tumors of the Uterus, Tr Am Obst Soc **38** 481, 1913

20 Martin, in discussion of Strassmann and Lehmann (footnote 13)

21 Romberg, E. Lehrbuch der Krankheiten des Herzens und der Blutgefasse, ed 4, Stuttgart, F Enke, 1925, pp 99, 242, 248 and 500

22 von Jaschke, in Frankl-Hochwart, L. Die Erkrankungen des weiblichen Genitales in Beziehungen zur inneren Medizin, Vienna, Alfred Holder, 1913, vol 1, p 58

23 Walthard, M, in Menge and Opitz. Handbuch der Frauenheilkunde, ed 1, Wiesbaden, J F Bergmann, 1913, p 170

24 Fleck, G. Myom und Herzerkrankungen in ihren genetischen Beziehungen, Arch f Gynak **71** 258, 1904

25 Neu. Experimentelles und anatomisches zur Frage des sogenannte Myomherz, Zentralbl f Gynak **2** 1532, 1911

26 Herz, M. Kropfherz, Myomherz, Klimakterium, Wien med Wchnschr **22** 517, 1913

27 Mahler, J. Myomherz und tiefen Therapie Med Klin **14** 588, 1914



in the cardiovascular system E Strassmann<sup>28</sup> expressed the belief that some deleterious agent acted on the uterus to produce the tumor and on the heart and blood vessels to cause fibroid, fatty and other damaging changes in the heart muscle and the hypertensive state Still others implicated the ovaries as the cause of the picture of disturbed action of the heart

Von Muller<sup>17</sup> thought that such uterine disease could initiate and propagate the hypertensive state found in the later decades, but no other authorities seem to have agreed with this view Polak, Mittel and McGrath,<sup>29</sup> in a study of blood pressures in patients with fibromyoma of the uterus, could not demonstrate that hypertension was definitely related to the occurrence of the neoplasm

The question of whether the tumor itself can produce substances harmful to the heart has been investigated by Thalheim and Birnbaum<sup>30</sup> with chemical methods and by Patta and Decio<sup>31</sup> with injections of extracts of the fibroids into animals No definite conclusions accrued

Other beliefs, now more or less ignored, were that the tumor does harm by compressing blood vessels, ureters and other abdominal structures, by impeding the flow of blood through the uterus, by pressing on the sympathetic plexuses and indirectly by producing pain Uncommon occurrences such as encroachment on the position and movements of the diaphragm and massive degenerations of fibroids have to be admitted as real, though secondary, causes of disturbance of the heart

Though a direct cause and effect relationship has not been demonstrated, there exist mechanisms, secondary in initiation and nature, that can more or less readily be held to account for the existence of heart disease in patients with fibromyoma of the uterus Prominent among them is anemia caused by repeated uterine hemorrhages, at or between the menstrual periods and thus conditioned by the tumor The anemia, by virtue of its damaging influence on the heart muscle, could bring about cardiac failure This is truly a secondary effect, as it can be observed in other forms of hemorrhage This view of the mechanism of myocardial insufficiency is advocated by Winter,<sup>18</sup> Kelly and Cullen,<sup>14</sup>

28 Strassmann, E Die Kreislaufänderung durch Klimakterium und Kastration bei Myom, Arch f Gynak **126** 169, 1925

29 Polak, J O , Mittel, E A , and McGrath, A B What Is the Relationship of Hypertension to Fibroid Tumor of the Uterus? Am J Obst & Gynec **4** 227 (Sept ) 1922

30 Thalheim and Birnbaum Untersuchungen über die chemische Zusammensetzung der Myome und der Uterus Muskulatur, Monatschr f Geburtsh u Gynak **28** 510, 1908

31 Patta, A , and Decio, C Ueber die Beziehung des Uterusmyom und Kreislauf, Monatschr f Geburtsh u Gynak **34** 548, 1911

Walthard,<sup>23</sup> McGinn<sup>10</sup> Healy,<sup>11</sup> Engelmann,<sup>32</sup> Martin<sup>20</sup> and Romberg<sup>21</sup> It is also the one most frequently presented in current textbooks of gynecology and internal medicine<sup>23</sup>

In the case of a patient presenting severe anemia and heart failure, an occasion was afforded to test clinically the truth of the assumption of the injury of the heart by anemia. The patient was studied with more than the usual care in ordinary hospital observation, frequent hematologic studies (red and white blood cell counts and estimations of hemoglobin), chemical determination of the blood (essentially plasma protein and urea) and electrocardiographic and teleoroentgenographic studies were made. Figures 1 and 2 show the alterations observed with the aid of these methods. The whole course of observation covered a period of about thirteen months and includes, besides the preliminary hospitalization, a number of return visits for complete reexamination.

#### REPORT OF A CASE

*History*—Mrs. C. V., aged 39, a housewife, was first seen on Aug. 10, 1930, at the Albert Merritt Billings Hospital. The family, childhood and other past history was unimportant. Two years previous to admission, there was a left peritonsillar abscess of ten days' duration. She had had three normal pregnancies and deliveries. The third, eight years previously, seemed to mark the beginning of the present illness. The menstrual process, which was normal before the onset of pregnancy, was accompanied by a progressively increasing amount of bleeding at each period, and within the month before admission to the hospital, by gushes of blood from the vagina with each effort of defecation. At the later periods, it was estimated that as much as a pint of blood was lost. The course was one of progressive invalidism, consisting of breathlessness, sensations of pounding and pain in the left anterior thoracic region and consciousness of rapid beating of the heart. Formerly these came with the slightest exertion, but in the three days before admission they occurred spontaneously and were severe enough to require absolute confinement in bed. Furthermore, there was persistent and increasing swelling of the legs, eyelids and right arm.

32 Engelmann. Beobachtungen über Myome der Gebärmutter, Arch. f. Gynäk. 76: 133, 1905.

33 Graves, W. P. Gynecology, ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 143. Miller, C. J. An Introduction to Gynecology, ed. 1, St. Louis, C. V. Mosby Company, 1931, p. 194. Lynch, F. A., and Maxwell, A. P. Pelvic Neoplasms (Gynecologic and Obstetrical Monographs), New York, D. Appleton and Company, 1931, vol. 10, p. 100. Anspach, B. M. Gynecology, Philadelphia, J. B. Lippincott Company, 1927, p. 302. Kulbs, F., in Mohr and Staehlin. Handbuch der inneren Medizin, Berlin, Julius Springer, 1928, vol. 4, p. 581. Curtis, A. H. A Text-Book of Gynecology, Philadelphia, W. B. Saunders Company, 1931, p. 72. Crossen, H. S. Diseases of Women, ed. 7, St. Louis, C. V. Mosby Company, 1930, p. 572. Vaquez, H. Diseases of the Heart, translated by G. F. Laidlaw, ed. 1, Philadelphia, W. B. Saunders Company, 1924, p. 451. Special mention of the excellence of the discussion of the association of heart disease and fibromyoma of the uterus by H. Albrecht (footnote 2) should be made here.

As far back as the onset, the patient had been informed of having anemia and had received frequent intravenous injections of solutions of ferrous salts, without relief

*Examination*—When first seen, the patient was sitting upright in bed and breathing rapidly and with effort. An extensive edema, principally in the soft

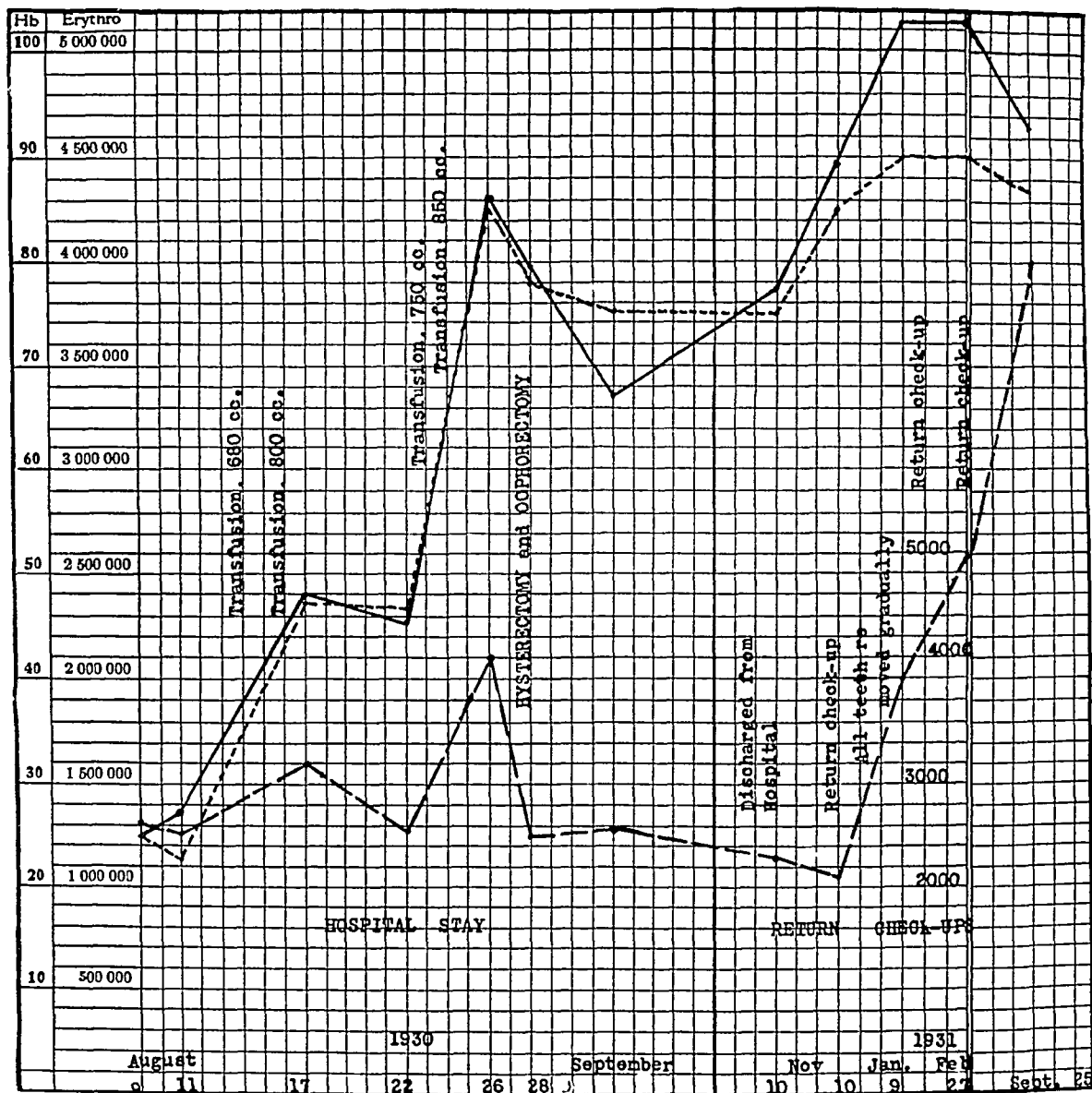


Fig 1—Chart showing relationships between red and white blood cell counts and percentage of hemoglobin and transfusions. The short dash line indicates hemoglobin in per cent, the continuous line, the red cell count in millions, and the long dash line, the white cell count in thousands.

tissues of the face, the right arm and the lower part of the back and legs was present. There were marked gingival exudation and dental caries.

Examination of the chest showed dullness to percussion over the base of the right lung and corresponding regional suppression of breath sounds, with crepitant

and moderately coarse râles. The maximum apex impulse was diffuse, and was felt in the anterior part of the left axilla in the fifth interspace. A loud, rough, systolic murmur was heard constantly over the region of the maximum apex impulse. The blood pressure was 160 mm of mercury systolic and 80 diastolic. Abdominal palpation revealed a firm, tender, nodular and somewhat fixed ovoid

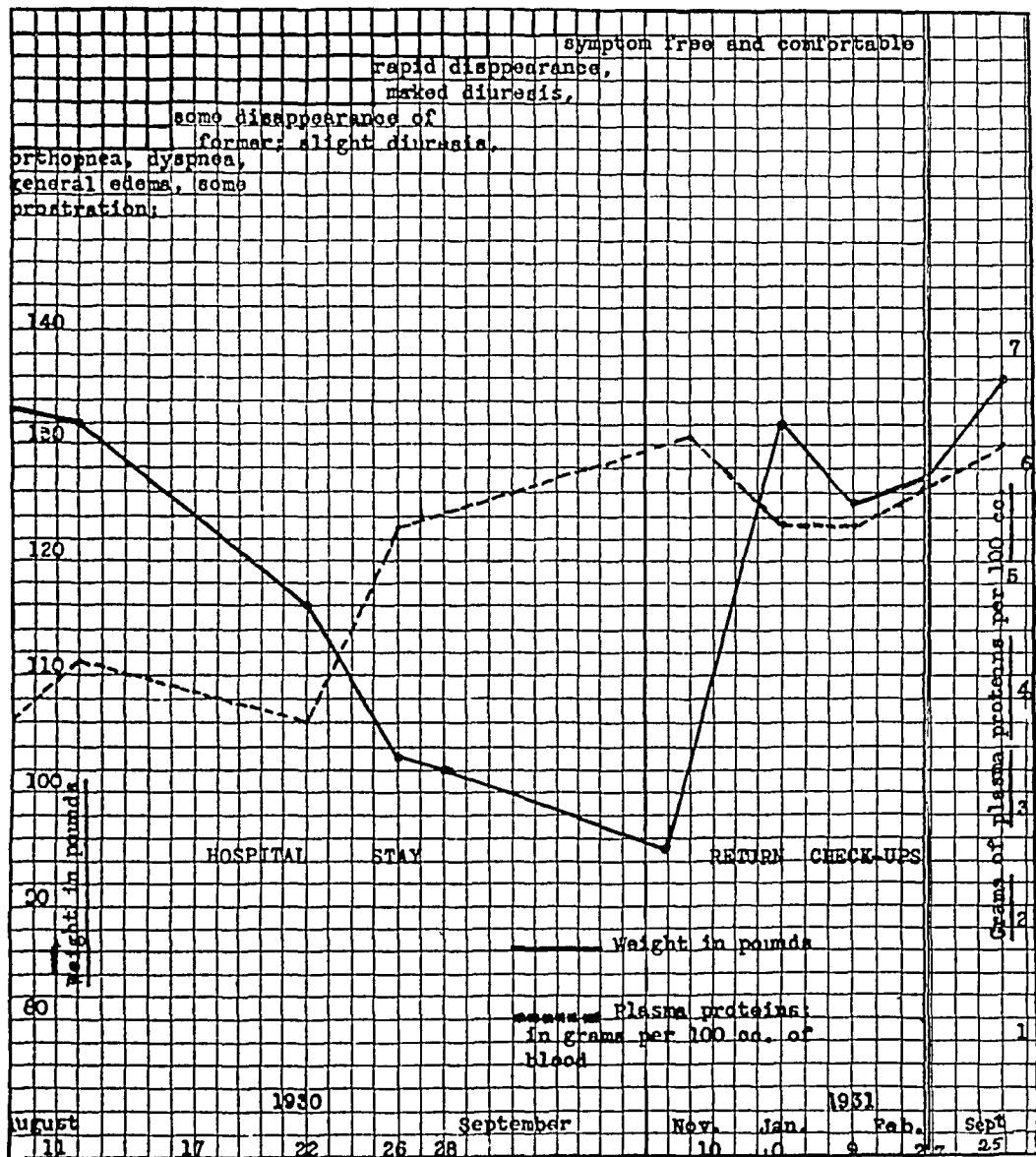


Fig 2—Chart showing relationship between weight and plasma proteins and the variation in certain symptoms. The blocks indicate the severity of the symptoms.

mass projecting 10 cm above the symphysis of the pubis in the midline. Pelvic examination demonstrated the mass to be a part of the uterus.

Marked secondary anemia and leukopenia (changes in the hematologic observations during the course of the illness are shown in fig 1), albuminous urine of low concentration, a diminished amount of plasma protein and low concentrating power of the kidneys (as measured by the ability to clear the blood of urea) were

found in the first laboratory examinations. According to a teleoroentgenogram, the heart was greatly and generally oversize, with a configuration suggestive of mitral stenosis. The waves of the electrocardiogram were of low amplitude. (The teleoroentgenograms and electrocardiograms are shown in figure 3.)

The temperature before operation varied between 99 and 101 F, but occasionally it was as high as 102.5 F. The pulse rate usually varied from 90 to 140, and the respiratory rate, from 22 to 40. All three varied almost directly with the degree of the symptoms and signs described.

*Diagnosis*—A diagnosis was made of large, bleeding and possibly infected fibromyoma of the uterus, mitral stenosis with myocardial hypertrophy and dilatation, severe anemia, generalized edema (including right hydrothorax) and severe oral sepsis. Chronic glomerulonephritis, active endocarditis and general sepsis were also considered.

On August 14, 16, 23 and 24, 680, 800, 750 and 850 cc of blood were transfused into the patient by the citrate method, with practically no ill effects, except one short chill. By August 17, the difficulty in breathing and other discomfort had disappeared. The edema, as indicated by the weight and physical findings (fig 2), was rapidly disappearing. Diuresis was copious. The amount of plasma proteins, the degree of renal concentrating power and the urinary changes progressed more slowly to normal. Though the red blood cell count and the hemoglobin value were nearly normal by the fourth week in August, leukopenia was still present. A slight decrease in the size of the heart and an increase in the amplitude of the waves were present in the teleoroentgenograms and electrocardiograms, respectively.

*Operation*—On August 27, supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed by Dr F. L. Adair under a combination of local infiltration and ethylene anesthesia. Somewhat more than the usual technical difficulties were experienced. The postoperative course was smooth. The patient was discharged on September 10 as much improved. At this time, she could have readily been ambulant, but she was kept to a rather vigorous regimen of rest.

*Course*—In four subsequent returns for further study, on Nov 10, 1930, and on Jan 9, Feb 27 and Sept 25, 1931, the patient reported progressive improvement. She was able to do light housework. The white blood cell count was normal on the last two visits. All teeth had been extracted and plates substituted. The right border of the heart had receded to the right edge of the sternum, and the left was usually about from 9 to 9.5 cm from the midsternal line in the fifth interspace. In the last visit, the left border of the heart was 8.5 cm from the midsternal line. Rough systolic murmurs were heard over the apical and aortic regions, but they were less loud than before. They have been present throughout the period of observation.

The series of teleoroentgenograms presented a heart of increasingly normal configuration and decreasing size, but never entirely normal. The electrocardiograms displayed progressive increase in the amplitude of the waves.

In the final return, the patient mentioned that she had begun to notice a tendency to consciousness of increased heart rate, occurring with exertion and spontaneously. The condition is being further investigated.

*Pathologic Report*—The uterus removed at operation measured 11 by 15 by 17 cm. It was symmetrically enlarged, nearly globular and contained an egg-shaped sac of a thick-walled and pedunculated submucous fibromyoma, measuring approximately 10 cm in various diameters. The contents of the sac consisted of necrotic and hemorrhagic material.

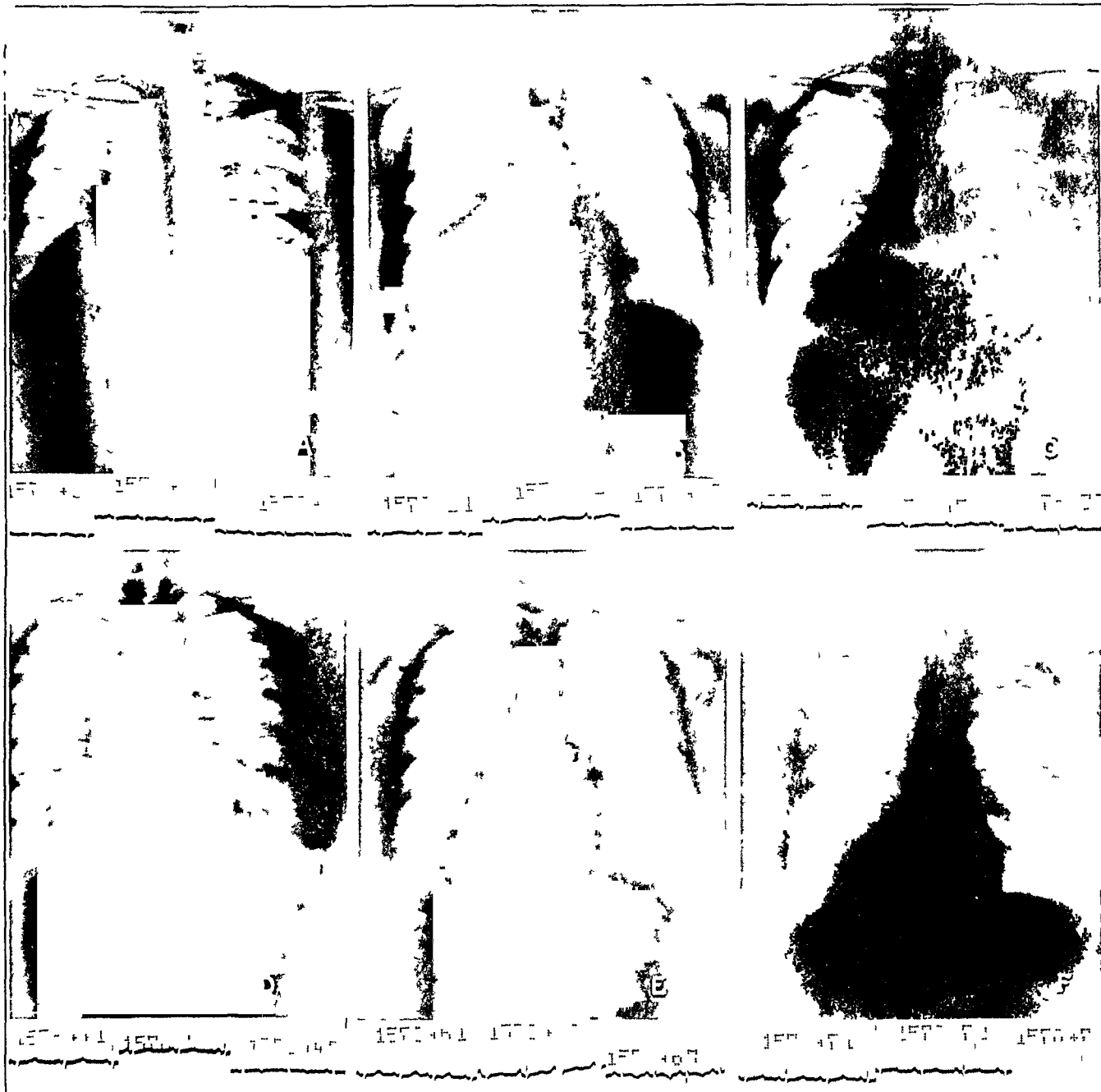


Fig 3—Showing electrocardiographic and teleoroentgenographic alterations *A*, taken Aug 11, 1930 (Mitral disease?) The heart is 65 per cent oversize, there is pulmonary congestion. Electrocardiographic curves are of low amplitude. *B*, taken August 25, shows condition unchanged from first picture. There is a tendency toward left axis deviation, the waves were slightly more increased in amplitude. *C*, taken September 8, shows heart now decreased to 40 per cent oversize. Waves are of slightly greater amplitude, left axis deviation remains. *D*, taken November 10, shows heart 25 per cent oversize. *E*, taken Feb 26, 1931, shows size of heart 24 per cent over normal. *F*, taken Sept 25, 1931, shows heart 31.4 per cent oversize. The electrocardiogram is unchanged in the last three pictures.

Microscopically, there were edema, hyalinization and shrinking of the muscle fibers and considerable deposition of dense collagenic connective tissue in the substance of the fibromyoma

## COMMENT

The rapid amelioration of the symptoms and signs during the course of rapidly repeated transfusions and the subsequent restoration of the condition of the blood to nearly normal, argues strongly, if only presumptively, that the anemia alone was responsible for the heart failure. The clinical picture, so far as the heart is concerned, can be explained on the basis of two types of activity imposed by the anemia. The first and early one involves the necessity of the use of the reserve function. According to Blumgart, Gargill and Gilligan,<sup>34</sup> from a study of the cardiac output in patients with anemia, there are an increased unsaturation of the hemoglobin, of minor importance, and an increase of cardiac output. The observation of increased cardiac output in the presence of experimentally produced hemorrhage in dogs has been noticed by Blalock and Harrison.<sup>35</sup> Along with the increased output of the heart there is a dilatation of the muscular wall. This is in no sense an indication of diseased muscle, but one of the manifestations of the process of compensation. The enlarged heart of this type returns rapidly to normal when the anemia disappears. The second type of activity represents the exhaustion of the reserve function and genuine damage to the myocardium, so that real heart failure supervenes. Anatomically, the heart muscle has been shown to present fatty changes and cloudy swelling. All of these changes have been well discussed by Walthard.<sup>23</sup>

In a search through the literature, there seems to be no mention of other cases as thoroughly investigated as the one of Ball.<sup>36</sup> The clinical, hematologic, teleoroentgenographic and electrocardiographic features were very much like those in the case that I have reported. A difference to be noted was that, though Ball's patient was first thought to have organic mitral stenosis, she presented a normal heart at the end of eleven months' of observation, in the patient discussed in this paper, probable mitral and possible aortic valvular lesions persisted, as residues, after the disappearance of the symptoms and signs. Ball gave a com-

34 Blumgart, H. S., Gargill, S. L., and Gilligan, D. R. Velocity of Blood Flow and Other Aspects of Circulation in Patients with "Primary" and Secondary Anemia, *J. Clin. Investigation* 9: 679 (Feb.) 1930.

35 Blalock, A., and Harrison, T. R. The Regulation of Circulation. V. The Effect of Anemia and Hemorrhage upon the Cardiac Output of Dogs, *Am. J. Physiol.* 80: 157 (March) 1917.

36 Ball, D. Changes in Size of the Heart in Severe Anemia, *Am. Heart J.* 6: 517 (April) 1931.

prehensive review of the literature dealing with clinical and other observations of the size of the heart in the presence of anemia

From the teleoroentgenograms, it will be observed that early changes were much greater than later ones. The early ones are attributable to the rapid decrease of the anemia, the later possibly to the regimen of rest. It was thought that the shape of the heart in either of the first two photographs might be due to a pericardial effusion, which disappeared, like the fluid elsewhere in the body, during the period of recovery of the heart.

The increase in the amplitude of the waves in the electrocardiograms was interpreted as due to improved oxygenation of the myocardium.

The edema has a complex origin. It is directly referable to the failing heart, to the impoverished kidneys in the presence of the defective circulation and to the deficiency of the plasma proteins secondary to the loss of blood plasma. Through clinical and animal experimental investigation it has been demonstrated by Leiter,<sup>37</sup> Barker and Kirk,<sup>38</sup> Bruckmann and Peters,<sup>39</sup> Frisch, Mendel and Peters<sup>40</sup> and Bennett, Dodds and Robertson<sup>41</sup> that edema may occur exclusively in the presence of diminished plasma proteins. The rapid loss of edema and body weight (as indicated by fig. 2) may be due predominantly to replacement of the plasma protein as a result of the transfusions.

Since the heart had preexistent anatomic lesions, it was all the more sensitive to the effects of diminished hemoglobin and protein contents of the blood.

Other factors that may have influenced the illness of the patient were the severe infections about the teeth and the extensive suppuration of the tumor.

#### CONCLUSIONS

1. The case of a patient with severe anemia, heart failure, edema and fibromyoma of the uterus is reported, together with graphic representations of the changes in the hematologic and chemical conditions of the blood and teleoroentgenograms and electrocardiograms.

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37 Leiter, L. Experimental Edema, *Proc Soc Exper Biol & Med* **26** 173 (Oct) 1928, Experimental Nephrotic Edema, *Arch Int Med* **48** 1 (Aug) 1931.

38 Barker, M. H., and Kirk, E. J. Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, *Arch Int Med* **45** 219 (March) 1930.

39 Bruckmann, F. S., and Peters, J. P. The Plasma Proteins in Relation to Blood Hydration, *J Clin Investigation* **8** 591 (June) 1930.

40 Frisch, R. A., Mendel, L. B., and Peters, J. P. The Production of Edema and Serum Protein Deficiency in White Rats by Low Protein Diets, *J Biol Chem* **84** 167 (Oct) 1929.

41 Bennett, T. I., Dodds, E. C., and Robertson, J. D. Plasma Protein Loss with Edema but Without Proteinuria, *Lancet* **2** 1006 (Nov 8) 1930.



2 It is shown that the heart failure disappeared rapidly and nearly completely as the result of the abolition of the anemia by transfusions and operation

3 The anemia, through its injurious effects on the heart muscle, causes compensatory changes in the heart, namely, an increased output per minute and dilation of the cavities, and later, as the cardiac reserve is exceeded, complete myocardial insufficiency

4 The importance of the deficiency in plasma proteins in relation to the causation of edema is indicated

5 Various views of the nature and cause of heart disease found in association with fibromyoma of the uterus are briefly discussed

6 There exists no proof that fibromyoma of the uterus can directly injure the heart

Dr L. Leiter, Dr F. L. Adair and Dr J. C. P. Fearrington assisted in the preparation of this paper

# HYPERPARATHYROIDISM WITHOUT PARATHYROID TUMOR

REPORT OF A CASE IMPROVED BY PARTIAL PARATHYROIDECTOMY

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AND

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The patient whose clinical record follows presented certain features that have recently been grouped together in the syndrome of hyperparathyroidism. She came under observation bedridden because of pain in the bones and muscular weakness. Examination disclosed extensive decalcification of the skeleton and an abnormally high blood calcium with excessive daily calcium output. Parathyroid tumor was searched for and none found. Removal of one apparently normal parathyroid gland produced no change in the symptoms or laboratory findings. When the surgeon, however, subsequently excised two similar anatomically normal glands on the opposite side, symptomatic improvement and a remarkable recalcification of the skeleton followed. The patient developed tetany postoperatively, which, however, gradually became more and more easily controlled, so that, twenty-two weeks after entry, she could be discharged competent to reenter her household routine. It is to emphasize the clinical significance of hyperparathyroidism without tumor that this case is being reported.

A brief resume of the evolution of present knowledge of hyperparathyroidism is necessary in introducing this record. The relationship between the parathyroid glands, calcium metabolism and pathologic conditions of bone has been proved within the last six years. Previous to 1925, the physiology of parathyroid tissue being obscure, medical science approached the syndrome now recognized as hyperparathyroidism by describing merely its end-results. A pathologic entity known as generalized osteitis fibrosa cystica had been observed from time to time for thirty years after von Recklinghausen<sup>1</sup> had originally described it.

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Read before the Section on Medicine of the College of Physicians of Philadelphia, Oct 26, 1931

From the Medical Clinic of the Hospital, and the Metabolic Section of the William Pepper Laboratory of Clinical Medicine, of the University of Pennsylvania

1 von Recklinghausen, F. Ueber Ostitis, Osteomalacie und Osteoplastische Carcinose, *Festschrift Rudolph Virchow, zu seinem 71. Geburtstage*, Berlin, G. Reimer, 1891

Mention of coincident parathyroid tumor was made occasionally in the pathologic reports of osteitis fibrosa, but its significance was not suspected. Experimental study of the glands was devoted almost exclusively to the effects of extirpation. The complex calcium and phosphorus metabolism through which the parathyroid dyscrasia influenced the skeleton was unknown.

In 1925 the results of three important attacks on the problem began to appear. Collip<sup>2</sup> announced the discovery of the parathyroid hormone and the preparation of a potent extract. This made experimental study of parathyroid activity possible. Mandl<sup>3</sup> of Vienna proved the etiologic relationship of the glands to osteitis fibrosa cystica. He implanted parathyroid tissue in a patient who had osteitis, made him worse thereby, then removed the implant plus a parathyroid adenoma and cured his patient. Finally, Aub and his co-workers<sup>4</sup> were prosecuting a series of studies in mineral metabolism which have established the links by which the glands and the skeletal changes are related.

Clinical hyperparathyroidism in the light of present knowledge, may tentatively be divided into two types, the primary, with benign or, rarely, malignant tumor of the parathyroid gland, and the secondary, with functional hyperactivity and at times glandular hyperplasia. In the former case, the high serum calcium, negative calcium balance and decalcification of bone result as the number of active parathyroid cells increases. In the latter type, the etiology is not entirely clear. Hyperactivity is thought, however, to follow a prolonged low intake of calcium, in which the glands, to keep blood values normal, progressively remove calcium from the storehouses in the bones. The depletion of the bones may go on, as a result of this overcompensation, long after the actual need for the stored calcium has passed. When the parathyroid glands have failed to revert to normal activity and cortical as well as spongy bone has become greatly decalcified, symptoms appear.

The majority of reported cases of hyperparathyroidism have been well advanced when they reached competent medical hands. Nevertheless, wide variations in the roentgenologic picture of bone have been found, dependent chiefly on the two factors of duration and degree of glandular hyperactivity. It is thus clear that one must now consider

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2 Collip, J. B. Extraction of a Parathyroid Hormone Which Will Prevent or Control Parathyroid Tetany and Which Regulates the Level of Blood Calcium, *J. Biol. Chem.* **63** 395, 1925.

3 Mandl, F. Therapeutischer Versuch bei einem Falle von Ostitis fibrosa generalisata mittels Extirpation eines Epithelkörperchentumors, *Zentralbl. f. Chir.* **53** 260, 1926.

4 Albright, F., Bauer, W., Ropes, M., and Aub, J. C. Studies of Calcium and Phosphorus Metabolism, *J. Clin. Investigation* **7** 139, 1929.

osteitis fibrosa cystica generalisata as one manifestation of the late stage of an endocrine-metabolic disease

The treatment of the primary form of hyperparathyroidism is surgical removal of the tumor. In the six years that have followed Mandl's pioneer operation, successful results following excision of the tumor have been reported in sufficient number to establish the operation firmly.

On the other hand, reports of therapeutic removal of parathyroid tissue when no tumor is found are scarce. Richardson,<sup>5</sup> operating on the patient with osteitis studied by DuBois and co-workers<sup>6</sup> and Bauer et al.,<sup>7</sup> made adequate search of the parathyroid bed. He found no tumor, and thereupon removed two normal-appearing glands. There resulted some symptomatic but no metabolic benefit in what was a far advanced case. Dresser and Hampton<sup>8</sup> recently reported the therapeutic removal of two normal parathyroid glands without benefit to the patient. One cannot be certain from the report, however, that the whole parathyroid region was examined at operation for possible tumor. It is possible, furthermore, that in both these instances excision of a third gland would have brought the desired result. Leriche,<sup>9</sup> of Strasbourg, finding hypercalcemia in certain cases of ankylosing polyarthritis, removed in each case an apparently normal parathyroid gland with symptomatic benefit to the patient.

Only Ballin and Morse,<sup>10</sup> very recently, have removed normal glands in hyperparathyroidism with clinical success. As in the case presented here hyperplasia could not be detected by ordinary histologic examination.

#### REPORT OF CASE

*History*—E. L., an Italian widow of 42 years, entered the medical clinic of the Hospital of the University of Pennsylvania on Feb. 2, 1931, complaining of weakness and aching pain in the bones. The patient had been obese since childhood, but up to the present illness of the past four years had always considered herself

5 Richardson, E. P., Aub, J. C., and Bauer, W. Parathyroidectomy in Osteomalacia, *Ann Surg* **90** 730, 1929.

6 Harmon, E. E., Shorr, E., McClellan, W. S., and DuBois, E. F. A Case of Osteitis Fibrosa Cystica (Osteomalacia?) with Evidence of Hyperactivity of the Parathyroid Bodies, *J Clin Investigation* **8** 215, 1930.

7 Bauer, W., Albright, F., and Aub, J. C. A Case of Osteitis Fibrosa Cystica (Osteomalacia?) with Evidence of Hyperactivity of the Parathyroid Bodies, *Metabolic Study II, J Clin Investigation* **8** 229, 1930.

8 Dresser, R., and Hampton, A. O. Osteitis Fibrosa Cystica Generalisata with Hyperparathyroidism as Etiology, *Am J Roentgenol* **25** 739, 1931.

9 Leriche, R., and Jung, A. Position actuelle du probleme de la polyarthrite ankylosante et de son traitement par les operations parathyroïdiennes, *Lyon chir* **28** 408, 1931.

10 Ballin, M., and Morse, P. F. Parathyroidism, *Am J Surg* **12** 403, 1931, Parathyroidism and Parathyroidectomy, *Ann Surg* **94** 592, 1931.

healthy There was evidence that her diet for many years had been deficient in respect to calcium-containing foods and the fat-soluble vitamins, in that she had shunned milk, butter, cream and cheese, and had eaten little fish, meat, eggs or fruit Her diet had consisted mainly of starches and vegetables Five of six pregnancies had ended in miscarriage (induced?) The second pregnancy went to term The last miscarriage had occurred six years before entry, two years before the onset of the pain in the bones No other factor in the past history suggested syphilis, and the Wassermann reactions of the blood at various times recently had all been negative

At the onset of her illness, the patient was living the usual life of a housewife in marginal circumstances in a small New Jersey town Her husband and one child were well There was no mental or physical strain The onset was evi-

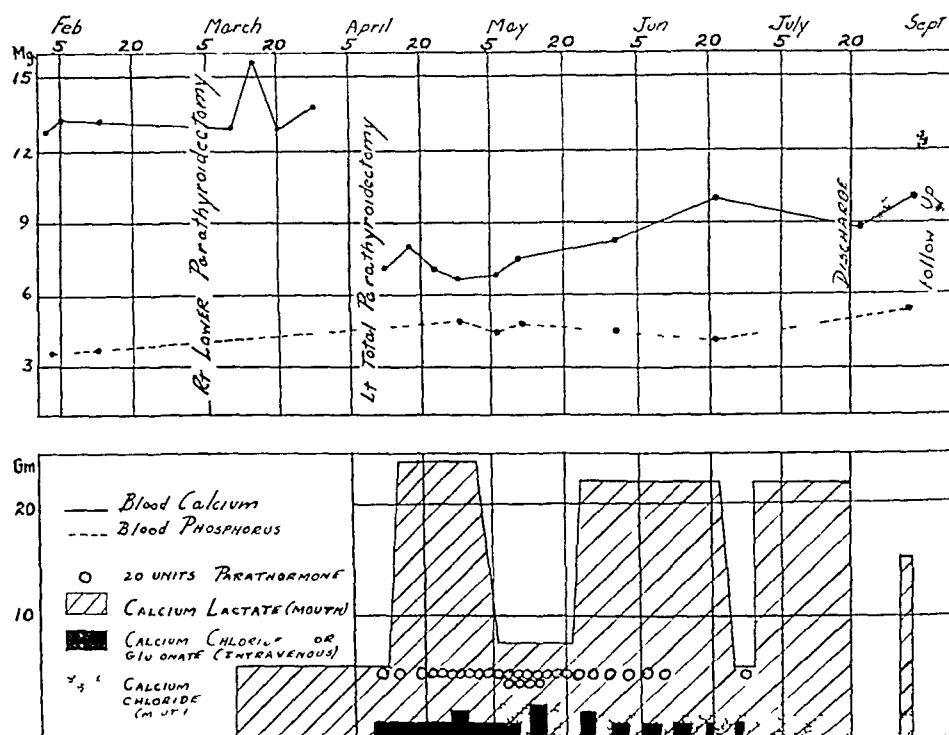


Fig 1—Chart showing the blood chemistry in correlation with the treatment in a case of hyperparathyroidism

dently gradual A dull, boring ache began in the legs and progressed until the patient hobbled about bearing as much weight as possible on her hands by taking hold of chairs, tables, etc., as she walked Several weeks before entry she became bedridden During the latter period, motion produced considerable pain, poorly localized, in any of the bones moved There was also increasing weakness

The discomfort had led the patient, one year previous to the clinic's acquaintance with her, to another hospital, where roentgenographic study of several bones was made The films, in the light of the present knowledge of the case, show definite generalized osteoporosis, at the time, they were considered to be imperfect films, and no diagnosis was made In November, 1930, ten weeks before entry, a second set of films showed, in addition, irregular areas of extreme decalcification, which led Dr Howard Curtis of Moorestown, N J, the patient's physician, to refer her to the University Hospital for study

*Physical Examination*—Examination on entry showed a short, obese Italian woman in considerable discomfort on motion even while in bed. Her family and friends readily agreed that she had grown shorter during her illness (as evidenced by the flattening of the vertebrae shown in the roentgenographic films). There was no kyphosis, however, no abnormal bowing of the long bones and no evidence of fracture. The muscles in general were hypotonic. There was moderate tenderness to pressure over the long bones. The teeth were in good condition.

No abnormality could be made out in the region of the thyroid gland, which was barely palpable. The electrical reactions of the muscles reached the highest



Fig 2—Roentgenographic appearance of the pelvis on admission. Note the transparency of the bone, the areas of extreme decalcification in the ilia and the narrowing of the bodies of the vertebrae.

normal limit, but they were not pathologically prolonged. Otherwise the physical examination showed normal conditions.

*Laboratory Findings*—The results of routine examination of the blood and urine were normal. The result of the test for Bence-Jones protein in the urine was negative. The basal metabolic rate was +11, which is within normal limits. The figures for blood serum calcium and inorganic phosphorus, on the other hand, are noteworthy. The serum calcium, by the modified Tisdall method,<sup>11</sup> was dis-

<sup>11</sup> Clark, E. P., and Collip, J. B. A Study of the Tisdall Method for the Determination of Blood Serum Calcium, with a Suggested Modification, *J. Biol. Chem.* **63**: 461, 1925.



Fig 3—Biopsy of the tibia, Mallory connective tissue stain,  $\times 18$  The loss of substance of the cortex, with widened marrow extensions, gives a spongy rather than compact appearance to the bone Compare the normal cortex shown in figure 4

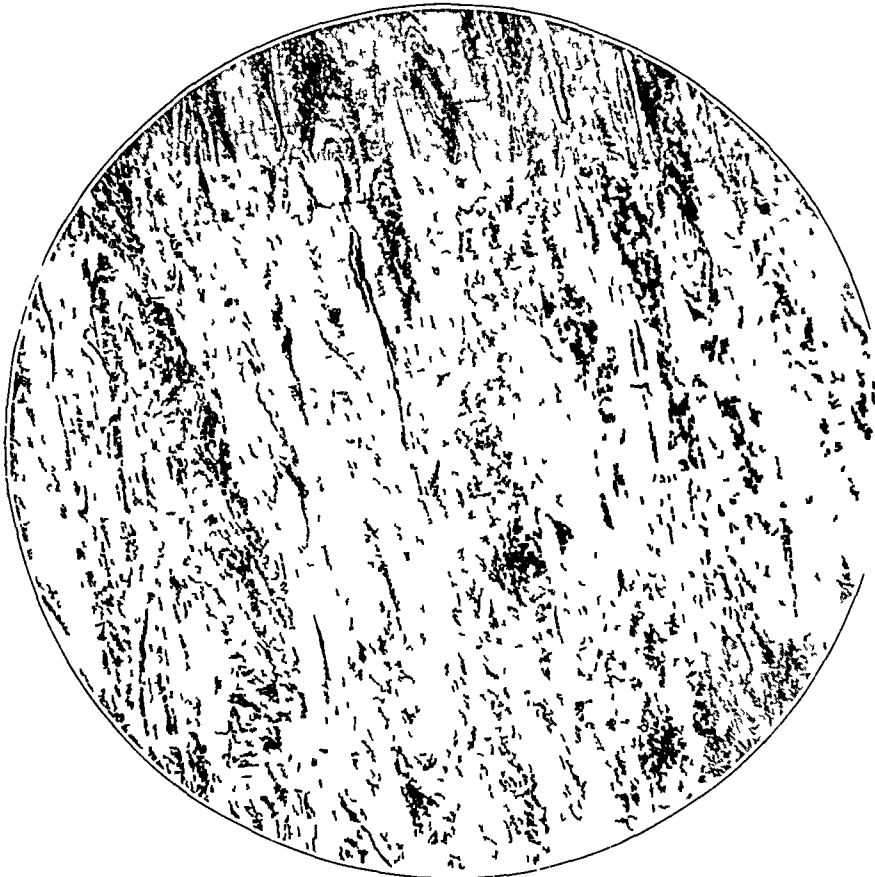


Fig 4—Normal cortex of tibia, Mallory connective tissue stain,  $\times 18$



Fig 5—Biopsy of tibia, iron-hematoxylin stain,  $\times 59$  Porous bone, with encroaching fatty marrow There is an increased amount of osteoid tissue, devoid of calcium, practically no cellular activity, either of osteoblasts or osteoclasts, is seen A few small foci of fibrosis in the marrow are found in study of the sections Occasional large wandering cells are to be found Compare the normal cortex shown in figure 6

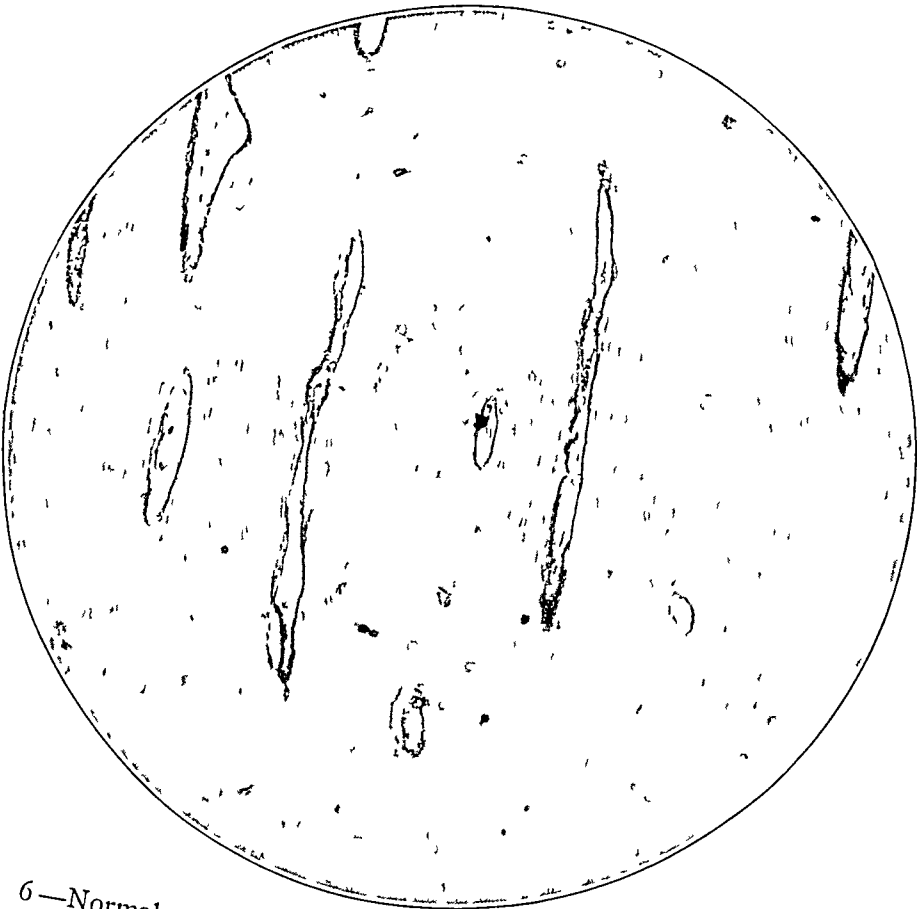


Fig 6—Normal cortex of tibia, hematoxylin-eosin stain,  $\times 59$



tinctly elevated to 127 and 132 mg per hundred cubic centimeters on two separate days. The blood phosphorus, determined by the method of Fiske and Subbarow,<sup>12</sup> was moderately lowered to 3.3 mg per hundred cubic centimeters.

The patient did not cooperate well in eating calcium-containing foods, but on a measured intake approximating 0.5 Gm of calcium daily, the urinary calcium in twenty-four hours amounted to 0.410 Gm, a figure above normal for that intake and indicating a negative balance. The figures for serum protein fell within the normal range. Variations in the significant laboratory data are indicated in figure 1.

*Roentgenologic Report*—The films of the patient's skeleton were examined by Dr. H. K. Pancoast and members of his staff with considerable interest. They were not typical of the usual roentgenograms of bone changes in generalized osteitis fibrosa cystica, probably because they were not of the advanced stage. They did show, however, rarefaction of all bones and narrowing of the vertebral bodies. There were multiple areas of localized extreme rarefaction in the pelvis, right femur and right humerus (fig. 2). Films of the urinary tract were negative for calculi.

*Clinical Course*—Surgical treatment was not instituted at once. Instead, the effects of a diet high in calcium and high in phosphorus (0.765 and 3.50 Gm daily, respectively), cod liver oil and heliotherapy were tried for one month. There was not the slightest improvement in symptoms or in laboratory findings. The patient was then transferred to the service of Dr. Charles H. Frazier, who explored the region of the right parathyroid glands, found nothing abnormal, and removed the parathyroid body at the lower pole. The gland was of normal size and histologic structure. The operation failed to alter the symptoms or the figures for calcium, and at the end of another month the roentgenologic picture of the bones was unchanged.

Five weeks after the first operation, the second parathyroidectomy was done. Dr. Henry F. Ulrich, assistant to Dr. Frazier, removed the left lobe of the thyroid gland in order to make certain of securing the parathyroid glands, which, two in number, were, like the first, of normal size and histologic structure.

On the third postoperative day tetany developed, as is not unusual in such procedures. The serum calcium, which had been 13.8 mg per hundred cubic centimeters just before operation, was determined during the first day of tetany to be 6.8 mg per hundred cubic centimeters, a tetanic level. The regimen instituted to control the tetany included large daily doses of calcium lactate (from 10 to 20 Gm), calcium chloride in 1 Gm doses given intravenously, as the attack developed, supplemented by calcium gluconate in doses of from 10 to 30 cc given intravenously or intramuscularly, and Collip's parathyroid extract (Parathormone-Lilly) in 20 unit doses, intramuscularly, about every second day. The diet high in calcium and high in phosphorus was continued, and the patient was given viosterol daily (fig. 1).

The roentgenograms of the bones three weeks after operation remained unchanged. A biopsy of the cortex of the right tibia was made in a region showing, roentgenographically, irregular areas of decalcification. Microscopic sections of this bone confirmed the diagnosis of osteoporosis, in a stage, probably, before generalized fibrosis had taken the place of the calcium-free bone matrix (figs. 3 and 5).

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<sup>12</sup> Fiske, C. H., and Subbarow, Y. The Colorimetric Determination of Phosphorus, *J. Biol. Chem.* **66**: 375, 1925.

The patient began to improve symptomatically from this point. She gradually needed less and less intravenous and intramuscular calcium and parathyroid extract to control the tetany. Two months after operation she was practically free from pain in the bones, felt stronger, and gradually began to move about, first in a chair and then on her feet.

More significant than all other indications of betterment, however, were the roentgenographic films, which, nine weeks after operation, showed a definite increase in deposit of lime throughout, the architecture of the bones was more distinct (fig 7). The figures for blood calcium and phosphorus were now within normal limits, 9.8 and 4 mg per hundred cubic centimeters, respectively. Incidentally, the basal metabolic rate did not fall as a result of the extirpation of one lobe of the thyroid gland.



Fig 7—Appearance of pelvic bones on June 16, nine weeks after parathyroidectomy. The shadow is generally darker, the irregular rarefied areas have disappeared.

Calcium medication now consisted of the lactate, an average of 20 Gm daily by mouth, 2 Gm of the chloride by mouth, and parathormone in 20 unit doses twice weekly.

The patient was discharged to her home on July 14, 1931, five and one-half months after entry, walking about without discomfort except for moderate lumbar pain, probably due to functional strain. She paid a follow-up visit to the ward in September, five months after operation. Further calcification of the skeleton was reported, the blood calcium and phosphorus were within normal limits, and the patient's calcium balance was positive. She remained free from tetany on a daily regimen of 15 Gm of calcium lactate and 2 Gm of the chloride by mouth.

## COMMENT

Certain points of the record merit emphasis as illustrating the variability in the picture of hyperparathyroidism

It is not known why this woman, whose childhood and youth were evidently normal, and whose adult life varied little from the ordinary, should develop at 40 an extensive osteoporosis. The recognized causes of osteoporosis were not operative, except perhaps a long-standing, mild dietary deficiency in foods high in calcium and vitamins A and D. One may speculate that the deficiency may have led to gradual overfunction of the parathyroid glands as they undertook to supply the body's calcium needs from the reservoirs in the bones. Marine<sup>13</sup> and Luce<sup>14</sup> demonstrated that a diet low in calcium will cause hyperplasia of the parathyroid glands in animals.

The three parathyroid glands that were removed showed no variation from the normal, by present criteria of judgment. In this connection one must keep in mind, however, that the size of the parathyroid gland varies considerably, and, as all observers agree, minor grades of hyperplasia may exist without being demonstrable by ordinary methods. It is not uncommon, moreover, in similar organs, for functional dyscrasia to exist without recognizable anatomic change, this may well occur in the parathyroid gland.

Decalcification here, as in other reported cases, was evidently slow. The symptoms, however, were more distressing than those usually found. That fact led to earlier hospitalization and treatment before decalcification had reached the stage of deformities and fractures.

The facts that removal of one parathyroid body had no effect on the symptoms and that all three glands were similar in size and structure suggest that all were equally involved. It was known that at least one parathyroid gland remained in situ after operation, and that in accordance with clinical and experimental evidence,<sup>15</sup> if tetany ensued, the remaining tissue would in time develop at least partial compensatory power. From the favorable course of the symptoms of tetany there is every reason to suspect that this occurred in the present instance.

The thought may arise that excision of a portion of the thyroid gland, rather than the parathyroidectomy, may have been responsible for the favorable result, for osteoporosis has been observed in certain

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13 Marine, D. Parathyroid Hypertrophy and Hyperplasia in Fowls, *Proc Soc Exper Biol & Med* **11** 117, 1913.

14 Luce, E. M. The Size of the Parathyroids of Rats and the Effect of a Diet Deficiency of Calcium, *J Path & Bact* **26** 200, 1923.

15 Tanberg, A. The Relation Between the Thyroid and Parathyroid Glands, *J Exper Med* **24** 547, 1916. Guy, C. E. Adenoma of the Parathyroid, *Arch Path* **3** 352 (Feb) 1927.

cases of hyperthyroidism by Aub and his co-workers<sup>16</sup> and others. All the available evidence, however, indicates that changes in the bones occur only in long-standing hyperthyroidism, which this patient certainly did not have. Furthermore, hyperthyroidism increases calcium output, but does not alter the calcium content of the blood. The serum calcium here was consistently high, and subsequent restoration of bone was demonstrably associated with the lowering of that figure.

#### SUMMARY

The foregoing clinical record represents a moderately advanced state of hyperparathyroidism in which medical measures failed to bring relief. Pain in the bones and extensive decalcification were prominent symptoms and led to hospitalization before the advanced skeletal disease, with fibrosis and cystic degeneration, had developed. There was no parathyroid tumor.

Surgical excision of one parathyroid body was of no apparent benefit. Subsequent removal of two of the remaining parathyroid bodies brought about a dramatic fall of the blood calcium, with tetany. As the severity of the tetany subsided there developed a remarkable recalcification of the diseased bone, progressing in five months to an essentially normal roentgenographic picture of the skeleton.

The result that followed removal of the three parathyroid glands left no doubt that in them lay the cause of the patient's illness. Hyperplasia was not demonstrable.

The course of this patient's illness indicates that, when clinical findings signify overactive parathyroid glands, surgical removal of considerable parathyroid gland tissue is justified, even though the operator sees no gross evidence of abnormality therein.

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<sup>16</sup> Aub, J. C., Bauer, W., Heath, C., and Ropes, M. Studies of Calcium and Phosphorus Metabolism. III. The Effects of the Thyroid Hormone and Thyroid Disease, *J. Clin. Investigation* 7:97, 1929.

# RELATIONS BETWEEN PRIMARY HYPOCHROMIC ANEMIA AND CHLOROSIS

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Under the designation of hypochromic anemia<sup>1</sup> (primary microcytic, idiopathic, achylic) there have appeared in the recent literature<sup>2</sup> a number of reports. They concern themselves with a disorder featured by an anemia with a low color index and small erythrocytes, and usually by gastric anacidity, which occurs almost exclusively in women in from the third to the fifth decade. The implication of most of the current writings is to the effect that this syndrome is a specific disease, some authors (Witts,<sup>3</sup> Dameshek,<sup>4</sup> Mills<sup>5</sup> and Vanderhoof and Davis<sup>6</sup>) have definitely stated that such is their belief. Furthermore, although this is admitted to be a chlorotic type of anemia, it is usually claimed that it is not chlorosis but rather an entirely distinct entity. That chlorosis, so common in the practice of physicians a generation ago, should have vanished and that a new type of chlorotic anemia should have appeared is a question of sufficient interest to justify critical discussion and my present purpose is not primarily to add further case reports to the literature of "hypochromic anemia," already well documented, but to analyze the evidence bearing on its claims to definite identity as well as on its relation to the disease chlorosis.

## IS THE "HYPOCHROMIC ANEMIA" OF CURRENT WRITERS A DEFINITE DISEASE?

Most of the recent reports trace the genesis of hypochromic anemia as a distinct entity to the work of Faber and of Faber and Gram,<sup>7</sup> who emphasized the frequent occurrence of anemia with a low color index

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1 Henceforth in this paper, for the sake of convenience, the condition will be referred to as "hypochromic anemia."

2 Waugh, T. R. Hypochromic Anemia with Achlorhydria, *Arch. Int. Med.* **47**: 71 (Jan.) 1931.

3 Witts, L. J. Simple Achlorhydric Anemia, *Guy's Hosp. Rep.* **10**: 253, 1930.

4 Dameshek, W. Primary Hypochromic Anemia, *Am. J. M. Sc.* **182**: 520, 1931.

5 Mills, E. S. Idiopathic Hypochromemia, *Am. J. M. Sc.* **182**: 554, 1931.

6 Vanderhoof, D., and Davis, D. Anemia of the Microcytic Type in Middle-Aged Women, *Tr. A. Am. Physicians* **46**: 284, 1931.

7 Faber, K., and Gram, H. C. Relations Between Gastric Achylia and Simple and Pernicious Anemia, *Arch. Int. Med.* **34**: 658 (Nov.) 1924.

in patients with gastric anacidity. There was nothing in Faber and Giam's paper, however, to indicate that they regarded this anemia as anything more than a "complication" of achylia, they pointed out that it was of a benign character, although it tended to recur, and that the response to an iron preparation was satisfactory. Without reviewing in detail the numerous subsequent studies, that have culminated in the recent concept of hypochromic anemia as a distinct disease, the features of the condition about which all writers agree may now be summarized

- 1 The disorder occurs almost exclusively in women
- 2 It is essentially a disease of middle life (from 30 to 50 years)
- 3 It is a mild chronic or relapsing disorder which does not directly lead to a fatal outcome
- 4 Symptoms, if present, are those of general lack of well-being and such non-specific disturbances as come with any anemia. The patients are usually not "physically fit"
- 5 The pallor is "white," and there is no icterus as in addisonian anemia
- 6 Gastric anacidity is characteristic
- 7 The blood shows an anemia with small cells and a relatively marked decrease in hemoglobin, and color indexes of 0.6 or lower are the rule
- 8 Megaloblasts are not present
- 9 There is no hyperbilirubinemia
- 10 The bone marrow is hyperplastic and is crowded with normal erythroblasts and normoblasts (Dameshek)
- 11 There is no demonstrable external cause, such as bleeding from abnormal sources
- 12 There is no improvement after the ingestion of liver, but the administration of iron or of iron and copper preparations is followed by a rapid increase in the hemoglobin and cell count

But no sooner has one laid down these criteria than exceptions and variations begin to appear in great numbers. The condition is not confined to women. Dameshek,<sup>1</sup> for example, among his seven cases reported an instance in a man of 29 years who, without demonstrable cause, had a severe anemia of the type under discussion. The hemoglobin was 42 per cent, the erythrocytes were 3,470,000, and the average red blood cell diameter was 6.14 microns. There was a prompt response to an iron preparation after liver had failed. The only atypical feature was the presence of free hydrochloric acid in the gastric secretion. Witts<sup>2</sup> also reported a case in a man, and I studied a young Japanese who had the trouble in typical form, including gastric anacidity after histamine. The disorder is not confined to middle age but may occur in young people. In Dameshek's case 3 a woman aged 23 years "had been more or less pale since infancy and had never been strong." In Mills'<sup>3</sup> case 8 the patient was 26 years old and had been anemic for ten years. In his case 1 the patient, although 40 years of age at the

time of the study, said she had "always" been anemic. In McCann's<sup>8</sup> case 1 the patient complained of "perpetual fatigue and pallor." "These symptoms dated from early childhood." McCann's case 3 was that of a young woman of 19 years. "For five years she was notably pale." There are also some aberrations in the physical findings. A number of patients are reported to have had papillary atrophy of the tongue, and this has been so twice in our own experience. In other reports (McCann and Dye<sup>8</sup>) splenomegaly has been stressed as a feature. All sorts of complicating disorders, infections and disabilities are described in various cases. Gastric anacidity is not constant, and even without the crucial histamine test a number of cases have been described in which free hydrochloric acid was present (Mills,<sup>5</sup> Dameshek<sup>4</sup> and Vanderhoof and Davis<sup>6</sup>). I have also studied a condition otherwise indistinguishable from the disorder under discussion except for the presence of normal gastric acidity. The statement commonly made that there has been no loss of blood must always be open to question when women are concerned. Such notes as "she developed increased menstrual flow, and at times would flow between periods" (Dameshek<sup>4</sup> case 1) are not uncommon, and even though the patient regards the flow as normal, she often has no valid standard of comparison.

A consideration of the preceding analysis would seem to make it clear that the "characteristic" features of hypochromic anemia are subject to so many exceptions that the greatest caution must be used in setting up this disorder as a specific disease. In support of this point of view I wish to quote my experience which includes, in addition to cases of the "typical hypochromic anemia" of current writers, patients who illustrate the following variations:

- 1 Patients with unexplained gastric anacidity in perfect health and with normal blood

- 2 Patients with unexplained gastric anacidity with all degrees of anemia (hypochromic), showing a gradation from a normal count to outspoken deficiency

- 3 Patients with severe anemia of the type under consideration but with slight degrees of gastric acidity

- 4 Patients with severe anemia of the type under consideration but with normal gastric acidity

The following cases illustrate these various types

CASE 1—*Unexplained gastric anacidity in a woman of 26 years without anemia*

Mrs. N. D. (case 199503), aged 26, a housewife, entered the clinic because of a variety of minor complaints. The family and past histories were not remarkable, although at times she had vague indigestion with gas. There was no special

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<sup>8</sup> McCann, W. S., and Dye, J. Chlorotic Anemia with Achlorhydria, Splenomegaly and Small Corpuscular Diameters, *Ann. Int. Med.* 4: 918, 1931.

menstrual abnormality. On examination she looked well and weighed 120 pounds (54.4 Kg). There were no abnormal physical findings. The stools were normal as were gastro-intestinal roentgenograms, but gastric analysis (histamine) yielded only small amounts of mucus with no free hydrochloric acid. Study of the blood showed red blood cells, 5,000,000, hemoglobin, 15.48 Gm or 90.3 per cent (Sahli), color index, 0.9, white blood cells, 14,250, polymorphonuclears, 77 per cent, cosmophils, 1 per cent, basophils, 2 per cent, lymphocytes, 15 per cent, monocytes, 5 per cent, platelets, 440,000, reticulocytes, 12 per cent, average red cell diameter, 7.65 microns, smear, normal.

*Comment*—This case is presented to emphasize one end of the series in contrast to the next group which will illustrate, in patients with anacidity, the gradual transition from normal blood to the outspoken syndrome of hypochromic anemia.

*Cases of Unexplained Anacidity with Various Degrees of Anemia*

Case	Patient	Age	Sex	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Comment
199503	D	26	F	5.00	90	0.9	Vague general complaints
A 9408	M	47	F	4.7	85	0.9	Clinical diagnosis psychoneurosis
197210	W	65	F	4.28	71	0.87	Mild indigestion for years
A 16760	We	54	F	4.30	69	0.8	Nervous breakdown
137042	T	41	F	3.23	60	0.9	Chronic arthritis
A 10982	A	36	F	3.41	40	0.60	Nervous breakdown menstrual flow scanty, some recent hemorrhoidal bleeding
181922	A	50	F	1.65	21	0.63	Excessive uterine bleeding for two years

GRADATIONS OF ANEMIA IN PATIENTS WITH GASTRIC ANACIDITY

Every grade of anemia may be associated with gastric anacidity and to illustrate this point the following cases have been selected from the files (table). The anacidity in every instance was classified as "unexplained", that is, it was an incidental finding in patients who had no evidence of either pernicious anemia or cancer of the stomach. Transitions from normal blood (patient D) to outspoken anemia of the "hypochromic" type of which case A10982 is a typical instance are shown. It would serve no purpose to add to the literature more cases of typical hypochromic anemia but the following instance in a young man seems worthy of record.

*CASE 2—Severe hypochromic anemia in a man of 29 years without evidences of loss of blood*

M. T. (case A 17347), a Japanese farm laborer, aged 29, entered the hospital with the complaint of weakness. The past history yielded no explanation for an anemic state, there had been no loss of blood, and the diet appeared adequate. For several years there had been increasing loss of weight and weakness. There were



no digestive symptoms. Examination revealed a small, well muscled man who did not appear very ill. There was marked pallor without any suggestion of icterus. The tongue was normal, the spleen was not palpable and there were no proprioceptive changes in the extremities. There were signs of an old inactive apical tuberculosis.

The Wassermann reaction was negative and the icterus index 6, the histamine test for gastric secretion showed complete absence of free hydrochloride acid. Roentgenograms of the gastro-intestinal tract were normal. Examination of the blood showed red blood cells, 4,640,000, hemoglobin, 51.7 per cent (8.8 Gm per hundred cubic centimeters), color index, 0.56, cell volume, 29, volume index, 0.732, white blood cells, 9,370, polymorphonuclears, young forms, 12 per cent and segmented forms, 66 per cent, eosinophils, 2 per cent, lymphocytes, 15 per cent, monocytes, 5 per cent, platelets, 464,000, reticulocytes, 1.3 per cent. A smear showed marked anisocytosis and poikilocytosis, and polychromasia. No normoblasts or megaloblasts were seen. The red cells varied in size from 4.37 to 11.25 microns.

*Course*—The patient improved rapidly on an iron preparation. Fourteen days after therapy was started, the blood showed red blood cells, 5,000,000, and hemoglobin, 75 per cent. The patient felt perfectly well.

*Comment*—Aside from age and sex this case is a typical instance of hypochromic anemia. It illustrates well the futility of the rigid criteria that have been arbitrarily laid down in the recent literature. Certainly the condition might with equal propriety be designated as "male chlorosis."

One may next turn to a different variant of the syndrome under discussion, namely, severe anemia of the hypochromic variety without gastric anacidity.

*CASE 3—Typical hypochromic anemia syndrome in a middle-aged woman with subacidity but without anacidity*

A woman (case A 4557), aged 45, entered the clinic with the complaint of weakness and palpitation. The past history was not remarkable except for the presence of hemorrhoids for years. There had been occasional slight bleeding from the rectum, but no excessive menstrual flow. For several months she had noted increasing weakness, fatigability and shortness of breath on exertion. She had fainted several times after standing for a long time. She said that there had recently been an increase of the hemorrhoidal bleeding. On examination, aside from pallor, nothing remarkable was made out. There were some internal hemorrhoids which did not bleed at the time of the proctoscopy.

The Wassermann reaction was negative, the icterus index 4.7, and after histamine stimulation the highest gastric acidity attained was only 30 (total acidity), the average normal by this procedure being about 100. Roentgenograms of the gastro-intestinal tract were normal. Examination of the blood showed red blood cells, 3,790,000, hemoglobin, 6.9 Gm per hundred cubic centimeters (40.5 per cent), color index, 0.53, white blood cells, 7,260, polymorphonuclears, 70 per cent, basophils, 1 per cent, lymphocytes, 24 per cent, monocytes, 5 per cent, platelets, 492,700, reticulocytes, 1.4 per cent. A smear revealed anisocytosis, poikilocytosis and polychromasia.

*Comment*—The anemia in this case clearly seems to be due, in part at least, to bleeding from hemorrhoids. However, aside from the presence of a small amount of acid in the gastric secretions, the picture that resulted is typical of hypochromic anemia.

CASE 4—*Typical hypochromic anemia syndrome in a woman with normal gastric secretion*

Mrs. E. D. (case A 16698), a clerk, aged 38, entered the hospital with the complaint of weakness. The past history was unimportant except for the fact that hysterectomy was done two years before for excessive menstrual bleeding. She had had hemorrhoids to a slight degree for years, but had not noticed any special bleeding. About a year before examination she began to feel weak. Since then great lassitude, palpitation and dyspnea on exertion had developed. Examination showed nothing remarkable aside from pallor. Through the proctoscope one could see some internal hemorrhoids, which were not extensive, there was no bleeding at the time.

The Wassermann reaction was negative, the stool showed no occult blood, and the histamine test revealed practically normal gastric secretion (highest acidity, 83). Examination of the blood showed red blood cells, 3,710,000, hemoglobin, 40 per cent, color index, 0.54, white blood cells, 6,600, polymorphonuclears, 53 per cent, eosinophils, 1 per cent, lymphocytes, 40 per cent, monocytes, 5 per cent. A smear revealed very pale red cells, with poikilocytosis and anisocytosis.

*Course*—A hemorrhoidectomy was done, following which the patient was given large doses of iron and ammonium citrate with, later, the addition of 60 mg. of copper sulphate daily. In seventeen days the hemoglobin was 84 per cent and the red cell count 5,270,000 and the patient felt perfectly well.

*Comment*—Bleeding from hemorrhoids may have played a part in precipitating the anemia in this case, although as far as could be determined the loss of blood was very slight. At any rate, aside from the normal gastric secretion, the picture was typical of hypochromic anemia and the characteristic response to iron and copper preparations was readily obtained.

In summary, the foregoing cases illustrate that variations of all sorts from typical hypochromic anemia are encountered, and that they blend insensibly with this typical picture. One may find cases of gastric anacidity with the condition of the blood varying from normal to extreme anemia, one may find cases of severe hypochromic anemia with anacidity, subacidity or normal acidity.

The preceding analysis and reports of cases seem to me incompatible with the concept of a specific disease, achylic hypochromic anemia. It must be admitted that the combination of anacidity and anemia not uncommonly occurs in middle-aged women, but the vast majority of achylic women are not markedly anemic nor do all anemic women by any means have achylia. It seems as if some special concatenation of circumstances is necessary to produce the full blown syndrome, but until much more is known about iron storage and metabolism, as well

as the conditions governing blood formation and destruction, it will serve no useful purpose to set up a definite disease on the basis of criteria to which so many and such obvious exceptions exist

# IS THE HYPOCHROMIC ANEMIA SYNDROME RELATED TO CHLOROSIS?

Most of the recent writers, with the exception of Adamson,<sup>10</sup> assert dogmatically that hypochromic anemia is entirely distinct from chlorosis. The principal arguments that have been advanced are (1) that the former occurs in middle-aged women, whereas the latter is confined to young girls, (2) that the "green" color of chlorosis is not seen in hypochromic anemia, (3) that chlorosis is never associated with as severe an anemia as is encountered in the "hypochromic" cases in adults and (4) that in chlorosis there is hyperacidity rather than anacidity. Some writers allege critical differences in symptomatology.

Many older clinicians (in conversation) cling in an almost sentimental manner to the idea that chlorosis is a highly specific disease, stressing always the characteristic (greenish) facies, the occurrence in undernourished young women with menstrual disorders, and the response to iron preparations. Naegeli<sup>11</sup> carried this to a naive extreme when, having arbitrarily laid down the dictum that chlorosis occurs only in women, he refused to accept identical cases in males because they were in the wrong sex. It seems in order, then, to turn to the actual descriptions and records in the literature in the attempt to clarify the subject.

*Age*—In his masterly article on chlorosis Albutt<sup>12</sup> emphasized the fact that the onset is usually at or shortly after puberty. He believed, however, that the disease occurs in later life, in which case it "is to be regarded as a relapse." Osler<sup>13</sup> also mentioned the occurrence of attacks in women of middle age. Witts,<sup>14</sup> under the heading of "Late Chlorosis," described a series of cases in women over 30 years old identical with his cases of hypochromic anemia except that acid was present in the gastric secretions. It appears, then, that as regards age, chlorosis and hypochromic anemia merge insensibly into one another. In the former the patient may have "relapses" in later life, with the latter the patients often give a story of anemia since childhood.

10 Adamson, J. D. Chronic Chlorosis, *Canad. M. A. J.* **24** 793, 1931.

11 Naegeli, O. *Blutkrankheiten und Blutdiagnostik*, ed. 5, Berlin, Julius Springer, 1931, p. 306.

12 Albutt, T. C., in Albutt and Rolleston. *System of Medicine*, London, 1909, vol. 5, p. 681.

13 Osler, W., in Pepper, W. *An American Text Book of the Theory and Practice of Medicine*, Philadelphia, W. B. Saunders Company, 1894, vol. 2, p. 196.

14 Witts, L. J. Late Chlorosis, *Guy's Hosp. Rep.* **11** 205, 1931.

*Sex*—Occasional cases in boys and men indistinguishable from chlorosis are recognized by various writers (Albutt, Osler). The subject was recently discussed by Witts<sup>15</sup>. He reported five cases in young men under the heading of "male chlorosis". The findings and the response to iron preparations are identical with those described in connection with "typical hypochromic anemia". It is of particular interest that both with hypochromic anemia in adults and with chlorosis, males are affected in about the same small proportion of cases, a fact which, if it has any significance, would tend rather to relate than to differentiate the two conditions.

*Symptoms*—It would serve no purpose to quote at length the actual descriptions of chlorosis as compared with hypochromic anemia. The reader can convince himself in a moment, by consulting Albutt<sup>12</sup> and Osler,<sup>13</sup> that the symptoms are identical. The evidences of anemia, weakness, breathlessness, palpitation and often digestive and menstrual disorders are stressed in both cases. One can find no point of distinction.

*The Green Color*—Absence of the traditional green color of chlorosis is stressed by modern writers in differentiating chlorosis from hypochromic anemia. One wonders, however, whether this green color ever had any real existence. Certainly the contemporary accounts of a generation ago make no claim as to its constancy. "It must be borne in mind, however, that in many patients undoubtedly chlorotic this sign (the green color) may not be marked" (Osler,<sup>13</sup> 1894). "Many of these patients bear in their features the classical sign of their malady, but not so all of them, not a few of them carry colour (chlorosis florida or rubra)"—Albutt,<sup>12</sup> 1909). Certainly the "green color" does not appear to be a sufficiently substantial point on which to base a fundamental differentiation of diseases, and one must remember that the so-called lemon yellow color of pernicious anemia stressed in the textbooks for years has assumed a somewhat mythical character, and at any rate is not seen nowadays.

*The Degree of Anemia*—Another alleged point of differentiation between hypochromic anemia and chlorosis lies in the claim that the degree of anemia is less marked in the latter. This statement is not, however, supported by the facts. Osler<sup>13</sup> referred to a case in Thayer's series in which the red blood count was 1,950,000 with 17.5 per cent hemoglobin. The average hemoglobin value in Thayer's sixty-three cases was 42.3 per cent, with an average red cell count of 4,090,000, and the fact of the matter, which is clearly brought out in the protocols in the literature, is that in both chlorosis and hypochromic anemia one may encounter slight, moderate or severe degrees of anemia. Furthermore, the morphology of the blood in chlorosis as described,

<sup>15</sup> Witts, L. J. Chlorosis in Males, *Guy's Hosp. Rep.* **10** 417, 1930.

for example, by Osler<sup>13</sup> is identical with the modern accounts of hypochromic anemia "If a drop of fresh blood be examined, the pallor of the individual corpuscles is at once apparent. There may be many poikilocytes, by which we mean deformed red globules assuming the most curious flask-like, hammer-shaped, or pyriform appearance."

*Gastric Secretion*—Witts and others insist on the gastric anacidity of hypochromic anemia as an essential point in the differentiation of this condition from chlorosis in which there is said to be an abundance of acid secretion in the stomach. I have already pointed out, however, that cases indistinguishable from hypochromic anemia but without anacidity not infrequently occur, and Witts,<sup>14</sup> under the heading of "Late Chlorosis," reported a series of eighteen such cases arbitrarily separated from the anacidity group on the basis of their gastric secretion. As to chlorosis in the older sense, whereas the statement is frequently made in textbooks that acid is present in abundance, actual data from individual cases are meager. The literature was reviewed by Arneth<sup>16</sup> who pointed out that various workers have found either abundant acid, a low acid content or anacidity. It appears, therefore, that with both hypochromic anemia and with chlorosis any type of gastric secretion may be found.

*Response to Iron Preparations*—The response to iron preparations appears to be identical in both chlorosis and hypochromic anemia. "Chlorosis is one of the few diseases of which the physician is a therapeutic master. A few weeks' administration of iron, together with an improved hygienic condition, usually suffice to restore a ruddy glow to the most pallid cheek" (Osler). Figure 8 in Osler's<sup>13</sup> article, picturing the rise of blood in a case of chlorosis from 1,900,000 to 5,100,000 after three weeks of iron therapy, is practically identical with many of the charts from recent papers on hypochromic anemia.

#### COMMENT

The first point that emerges from the preceding analysis is the impossibility of differentiating "chlorosis" in the nineteenth century sense from the hypochromic anemia of modern writers. Neither age, sex, symptoms, gastric analysis, hematologic examination nor response to iron therapy offer any tangible criteria for separating the two conditions. The next question is whether either disorder represents a truly specific disease or whether the cases classed as chlorosis and hypochromic anemia do not rather constitute a syndrome without fixed characteristics. The evidence seems overwhelmingly in favor of the latter view. That the syndrome manifests itself predominantly in women

<sup>16</sup> Arneth, J., Parallel laufende Magensaft- und Blut-Untersuchungen bei der Chlorose, Deutsche med. Wchnschr. **32** 666, 1906.

during the period from puberty to menopause is an unquestioned fact, and it seems reasonable, therefore, to suppose that menstruation is an important contributory cause. Granted that certain people have an abnormally feeble power of regenerating blood (whether this defective power is inherent or precipitated by inadequate diet or by other means), such a tendency would obviously be unmasked by menstrual bleeding especially if excessive. Menstrual bleeding is doubtless not the only factor, and loss of blood from hemorrhoids and peptic ulcer has also been stressed in the literature on chlorosis. The small number of cases of anemia of this general type in men is then, probably to be explained by the absence of periodic losses of blood such as occur in women. Gastric anacidity can be fitted into the picture by invoking the observations of Mettier and Minot<sup>17</sup> that iron is better absorbed or at least more effective when the gastroduodenal medium is acid. At any rate, the whole situation offers a fertile field for careful studies of iron metabolism and of blood regeneration, which will doubtless lead to an eventual solution of the problem.

#### CONCLUSIONS

- 1 Chlorosis and idiopathic hypochromic anemia cannot be differentiated into independent entities
- 2 Neither is a specific disease, but the cases represent a syndrome with many variations
- 3 The frequency of these types of anemia in women is probably conditioned by menstrual bleeding
- 4 An analysis of the literature and case reports bearing on these points are presented

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<sup>17</sup> Mettier, S. R., and Minot, G. R. The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastroduodenal Contents in Certain Cases of Anemia, *Am J M Sc* **181** 25, 1931

# RELATION OF PAIN OF PEPTIC ULCER TO GASTRIC MOTILITY AND ACIDITY

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The pain of peptic ulcer is usually ascribed to one of two causes gastric acidity or gastric hunger contractions Ginsburg, Tumpowsky and Hamburger<sup>1</sup> ascribed the pain of ulcer to the increased gastric tension and correlated the pain with gastric hunger contractions Carlson<sup>2</sup> also showed that the pain in ulcer was synchronous with hunger contractions Reynolds and McClure<sup>3</sup> examined patients fluoroscopically, and found no relation between the gastric contractions and the pain in ulcer Ortmayer's<sup>4</sup> observations related the pain to gastric acidity Palmer<sup>5</sup> studied the subject extensively and reported a definite relation of gastric acidity to pain in gastric and duodenal ulcer He found that the injection of 0.5 per cent hydrochloric acid into the stomach in patients with active sensitive ulcer usually produced the characteristic pain He later claimed this as a specific test for ulcer In a small group of cases Palmer was able to show the relation of the pain to gastric hunger contraction He concluded "Hydrochloric acid is the normal stimulus to the pain-producing mechanism of sensitive peptic ulcers Normal gastric peristalsis may be an adequate mechanical

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1 Ginsburg, H, Tumpowsky, I, and Hamburger, W W Contribution to the Physiology of the Stomach XXXV The Newer Interpretation of Gastric Pain in Chronic Ulcer, J A M A **67** 990 (Sept 30) 1916

2 Carlson, A J Contribution to the Physiology of the Stomach The Origin of Epigastric Pains in Cases of Gastric and Duodenal Ulcer, Am J Physiol **45** 81 (Dec) 1917

3 Reynolds, L, and McClure, C W Motor Phenomena Occurring in Normal Stomachs in the Presence of Peptic Ulcer and Its Pain, as Observed Fluoroscopically, Arch Int Med **29** 1 (Jan) 1922

4 Ortmayer, Marie Gastric Motor Activity in Patients with Peptic Ulcer, Arch Int Med **35** 423 (April) 1925

5 Palmer, Walter Lincoln The Mechanism of Pain in Gastric and Duodenal Ulcers I Achlorhydria, Arch Int Med **38** 603 (Nov) 1926, II The Production of Pain by Means of Chemical Irritants, *ibid* **38** 694 (Dec) 1926, III The Role of Peristalsis and Spasm, *ibid* **39** 109 (Jan) 1927

stimulus in very sensitive ulcers. Hydrochloric acid may sensitize both the sensory and motor gastric mechanisms." Previous observers<sup>6</sup> introduced various amounts of hydrochloric acid into the stomach, varying in strength from 0.5 to 2 per cent, but failed to produce pain in normal persons or in patients with ulcer. Hardt<sup>7</sup> reported that the distress of ulcer could be relieved by 0.3 per cent hydrochloric acid.

Hardy<sup>8</sup> used Palmer's test, applying it to persons suffering from epigastric pain regardless of the seat of the lesion. He reported a positive acid reaction in only 65 per cent of 155 cases of ulcer that he investigated. He also studied 73 patients in whom no local lesion was discovered. He reported a positive acid reaction in 45 per cent of these cases. His results show that the acid test is not specific for ulcer.

We studied epigastric pain in relation to gastric motility and gastric acidity in 22 patients, 12 of these had duodenal, and 2 gastric ulcer. Nine of this group were operated on. The diagnosis in all cases was made on the basis of history, symptoms, physical signs and positive roentgen observations. The 8 remaining cases consisted of 4 cases of disease of the gallbladder and chronic appendicitis and 3 cases in which the final diagnosis was neurasthenia. One patient was studied who had a typical history of ulcer, but roentgen examination showed no pathologic condition of the digestive tract, and a satisfactory diagnosis was never reached.

#### METHODS

The patients selected for study were placed on a general ward diet. On this diet, the pain of the patient continued as before he entered the hospital. The following tests were then made:

1. The acid test was performed according to Palmer's technic. This consists of preliminary aspiration of the contents of the stomach after a fast for at least twelve hours. Then 200 cc of 0.5 per cent hydrochloric acid is introduced into the stomach. After half an hour, if the patient feels no pain, an additional 200 cc of the acid is again introduced and the patient is observed for another half an hour. If he still feels no pain, the procedure is repeated a second time. If in the course of one and a half hours, with a total of 600 cc of acid in the stomach the patient feels no pain, the test is termed negative, but if at any time during the test the patient complains, the test is considered positive. We controlled our tests by repeating them with water instead of acid.

6 Lowenthal. *Berl klin Wchnschr* **29** 1188, 1892. Schmidt, J. E. *Mitt a d Grenzgeb d Med u Chir* **19** 278, 1909. Hurst, A. F. *The Sensibility of the Digestive Tract*, London, H. Frowde, 1911.

7 Hardt, L. L. J. *Pain in Active Pathologic Processes in Stomach or Duodenum*, *J A M A* **70** 837 (March 23) 1918.

8 Hardy, J. L. *The Role of Hydrochloric Acid in the Causation of Gastric Pain*, *Lancet* **1** 711, 1929.



in those patients who reacted positively to the acid. This eliminated the possibility of the production of pain by the accumulation of a volume of fluid in the stomach.

2 In cases of duodenal ulcer a further test was performed by injecting acid directly into the duodenum, 50 cc of 0.5 per cent hydrochloric acid was slowly injected and a period of ten minutes allowed to elapse. If no pain developed, the test was performed a second time, and if the patient was still comfortable a third test was tried. In cases in which pain developed, the experiment was repeated with water instead of acid.

3 The third type of experiment was done in order to study the effect of both gastric motility and gastric acidity on the production of pain. After fasting from twelve to eighteen hours, the patient swallowed two tubes: a Rehfuß tube through which fluid could be withdrawn and injected into the stomach and a tube with a condom balloon attached so that a record of gastric motility could be obtained according to the method suggested by Boldyreff and perfected by Carlson. The gastric contractions were recorded, and then the effect of withdrawing gastric juice or introducing acid or water was studied. In cases of duodenal ulcer this procedure was repeated whenever possible with the tube in the duodenum. This proved difficult, as inflation of the balloon in the duodenum produced nausea, causing its regurgitation into the stomach. However, the relation of gastric contractions to duodenal contraction has been studied by Ivy and Vloedman<sup>9</sup> and by Quigley and Solomon<sup>10</sup>. This type of experiment was repeated as often as the endurance of the patient permitted.

In interpreting the records obtained, the temperament and emotional state of the patient must be considered. Such emotions as fear or rage tend to inhibit gastric contractions (Carlson<sup>11</sup>). The more phlegmatic type of patient showed considerable gastric motility the first time the tube was swallowed, while the excitable patient showed no motility whatever. Usually after a few trials the patient lost his fear of the tube and motility ensued. In some cases the patient objected so strenuously to swallowing the tube that the test could not be repeated. In this type of case, the patient's reaction to acid could be studied, but no conclusion could be reached as to the relation of motility to ulcer pain.

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9 Ivy, A. C., and Vloedman, D. A. The Small Intestine in Hunger, *Am J Physiol* **72**: 99 (March) 1925.

10 Quigley, J. P., and Solomon, E. I. Action of Insulin on the Motility of the Digestive Tract. Action on the Human Duodenum, Action on the Colon of Dogs, *Am J Physiol* **91**: 488 (Jan.) 1930.

11 Carlson, A. J. The Control of Hunger in Health and Disease, Chicago, University of Chicago Press, 1916, p. 151.

## RESULTS

In considering our results, those obtained in cases of ulcer will be taken first

The patients were found to fall into two classes (1) those who had pain response to an acid stimulus but showed no pain in relation to gastric motility and (2) those who had no pain response to an acid stimulus but had pain during periods of gastric motility. One of each of these types will be considered in detail and the results in all cases tabulated

## TYPICAL CASES

**CASE 1**—A man, aged 37, entered the hospital on March 31, 1931, with a complaint of epigastric pain coming on from about one to one and a half hours after meals and also after midnight, it was relieved by soda or food. Sometimes after he ate fried or highly seasoned foods, the pain came on immediately after meals, to be followed within from a half to three quarters of an hour by vomiting. Relief followed vomiting. These symptoms had been present for about ten years.

The Ewald meal showed a free acidity of 61 and a total acidity of 76. Fluoroscopic examination and roentgenograms demonstrated a definite ulcerous defect of the lesser curvature of the stomach. The diagnosis was later confirmed by operation.

The patient was put on a full ward diet and his symptoms were watched. On April 4 the acid test was performed according to Palmer's method.

*Acid Test*—Preliminary aspiration yielded 5.5 cc of gastric juice, alkaline and bile stained. Then 200 cc of 0.5 per cent hydrochloric acid was introduced. Pain followed in five minutes, but was relieved by aspiration. The test was repeated with 200 cc of water, no pain resulted.

*Motility Test*—On April 8 preliminary aspiration yielded 30 cc of gastric juice with a free acidity of 0 and a total acidity of 2. The motility test gave negative results, but pain was present. Then 140 cc of fluid was aspirated showing a free acidity of 25 and a total acidity of 30. There was relief of pain on aspiration. One hundred and forty cubic centimeters of water was introduced, no pain was felt. The fluid was withdrawn in half an hour, and 140 cc of 0.5 per cent hydrochloric acid was introduced. Pain occurred in five minutes, this was relieved by aspiration.

*Third Test—Motility and Acidity*—On April 10 preliminary aspiration yielded 85 cc of alkaline juice. A study of contractions showed slow changes in tone but no contractions when pain came on and aspiration was performed. Free acidity was 25, total acidity, 35. Relief from pain followed, and when the patient had been free from pain for forty minutes, another sample of gastric juice was taken revealing a free acidity of 15 and a total acidity of 25. Another pain period occurred later. Fifty cubic centimeters of gastric juice was aspirated, showing a free acidity of 30 and a total acidity of 45, relief from pain followed aspiration. A painless period then ensued, and 80 cc of 0.5 per cent hydrochloric acid was introduced followed immediately by pain, aspiration was again performed, but no relief was obtained until sodium bicarbonate, 30 grains (1.9 Gm) was given.

In this case the pain seemed to depend on the acidity of the gastric content. All aspirations done during periods free from pain withdrew

gastric juice of low acidity, whereas all of those done during periods of pain withdrew a fluid with an acidity of 20 or over. The injections of acid always brought on severe pain. The pain showed no relation to the recorded gastric contractions.

In 8 of 15 patients with ulcer, pain occurred in response to the injection of hydrochloric acid and had no relation to the gastric motility.

CASE 2—Mrs. F., aged 29, was admitted to the hospital on March 3, 1931. She complained that for the last three years she had had attacks of pain lasting five days and occurring every three weeks. The pain was described as sharp, located in the umbilical region and radiating from there along the left costal margin to the axillary region. It came on about an hour after meals and at night, and was relieved by soda or milk and cream. For the last six weeks the pain had been present constantly and the patient frequently vomited, shortly after meals. Fluoroscopic examination revealed a large duodenal ulcer and the diagnosis was later confirmed by operation.

TABLE 1—*Results in Cases Showing Pain in Response to an Acid Stimulus*

Case	Type of Ulcer	Acid Test		Motility Test		Diagnosis Confirmed by
		Number Positive	Number Negative	Number Positive	Number Negative	
1	Gastric	3		2		Roentgenogram and operation
2	Duodenal	1		1		Roentgenogram and operation
3	Duodenal	3		1		Roentgenogram and operation
4	Duodenal	3				Roentgenogram and operation
5	Duodenal	3		1		Roentgenogram
6	Duodenal	4		2		Roentgenogram
7	Duodenal	3		2		Roentgenogram and operation
8	Duodenal	3		2		Roentgenogram and operation

The patient was put on a soft diet, on which her symptoms continued.

*Acid Test*—On preliminary aspiration 200 cc. of gastric juice with a free acidity of 25 and a total acidity of 35 was withdrawn. Then 200 cc. of 0.5 per cent hydrochloric acid was introduced, no pain was noted after one-half hour. Again 200 cc. of 0.5 per cent hydrochloric acid was introduced, no pain occurred after one-half hour. Two hundred cubic centimeters of 0.5 per cent hydrochloric acid was again introduced, after one-half hour no pain was felt. The patient was restless and tired.

*Acid Test*—On March 14, preliminary aspiration yielded 100 cc. of gastric juice with a free acidity of 35 and a total acidity of 45. A Rehfuß tube was inserted into the duodenum. Then 50 cc. of 0.5 per cent hydrochloric acid was injected slowly, after ten minutes no pain was felt. Fifty cubic centimeters was again injected, and after ten minutes no pain was noted. Again 50 cc. was injected and no pain was felt. The patient stated that she had not experienced pain at any time.

On March 17, during a period of pain, the gastric motility was studied. Because of the patient's disinclination to swallow two tubes, only one with the balloon attached was given her, therefore, no study of gastric acidity could be made. The record showed vigorous type I contractions (Carlson<sup>12</sup>), which occurred at intervals of about a minute. During every contraction the patient registered pain.

12 Carlson (footnote 11, p. 44)

Our experiments on this patient then showed no pain in relation to gastric acidity, but indicated that the pain depended on gastric motility, since it occurred simultaneously with each contraction of the stomach.

In 6 of the other patients with ulcer, pain occurred synchronously with gastric contractions and not in response to acid stimulation.

One case of ulcer confirmed by operation could not be classified in either group.

CASE 3—A man, aged 60, entered the hospital in July, 1930, complaining of epigastric pain coming on from two to four hours after meals, relieved by taking soda or food. Roentgenograms revealed a duodenal ulcer, and this diagnosis was later confirmed by operation. The patient was put on a milk and cream diet, but his pain continued.

On July 15, the acid test according to Palmer's technic was tried. Pain came on when the patient had 400 cc of acid in the stomach, one hour after the test was started. This is a positive response. Two attempts were made to study the gastric motility but were unsuccessful because, in spite of starvation for fourteen

TABLE 2—Results in Cases Showing Pain During Periods of Gastric Motility

Case	Type of Ulcer	Acid Test		Motility Test		Diagnosis Confirmed by
		Number Positive	Number Negative	Number Positive	Number Negative	
1	Duodenal		2	1		Roentgenogram and operation
2	Duodenal		5	3		Roentgenogram
3	Gastric		3	2		Roentgenogram and operation
4	Duodenal		3	3		Roentgenogram
5	Duodenal		2	2		Roentgenogram and operation
6	Duodenal		4	2		Roentgenogram

hours, hunger contractions of the stomach were completely absent. Nevertheless, the patient registered pain intermittently during the test. Aspiration during pain withdrew gastric juice ranging in free acidity from 15 to 19, with a total acidity always of about 30. Relief never followed aspiration. The introduction of from 200 to 400 cc of 0.5 per cent hydrochloric acid in no way changed the character of the pain.

The studies on this patient indicate that his pain was not related to motility. However, the tube was in the stomach and the ulcer in the duodenum. A partial obstruction of the pylorus made it impossible to pass the tube into the duodenum, so we cannot be certain that duodenal contractions were not occurring while the test was done. Studies on the relationship of gastric and duodenal motility, however, show that the contractions occur nearly together, so that one would scarcely expect constant spasms of the duodenum while the stomach remained relaxed for a period of two hours.

Not could the acid test be considered positive. Once, to be sure, it acted positively, but the patient volunteered the information that the pain, which was long delayed, was very slight. In cases in which the response to acid is late and is slight one doubts the value of the acid

test Presumably, a spontaneous pain might occur at such a time We have records that show that the inhibitory effect of the introduction of acid on the gastric contraction disappears within half an hour, so that a late pain response to acid might in reality be due to motility

In this case our studies show no relation between the pain of ulcer and either gastric motility or acidity

The case of a man who showed no lesion of the stomach or duodenum should be recorded because he reported two types of pain, one of which we related to gastric contractions and the other to high gastric acidity

CASE 4—This patient complained of hunger pain occurring after a long period without food Another kind of pain described as sharp and knifelike and located in the epigastrium occurred within an hour after eating The symptoms had been present for ten years The patient had lost 12 pounds (5.4 Kg) within the last year Fluoroscopic examination revealed no pathologic condition, and as an operation was not resorted to, the possible diagnosis of ulcer was uncertain

Palmer's acid test was first tried In a preliminary aspiration 12 cc of fluid was withdrawn with a free acidity of 10 and a total acidity of 25 Then 200 cc of 0.5 per cent hydrochloric acid was injected Within five minutes a sharp and knifelike pain came on, similar to the type of pain that the patient experienced after eating This pain was relieved by the administration of 25 grains (1.6 Gm) of sodium bicarbonate

A few days later, after a fasting period of twenty-four hours, the gastric motility was studied The patient was complaining of hunger pain at the time that the record was taken The gastric contractions were vigorous at first, and the patient registered pain simultaneously with each contraction or whenever the tonus was high A quiescent period came on, and the pain ceased At this time 100 cc of hydrochloric acid was introduced In five minutes the patient registered pain, which he described as the sharp epigastric pain that he usually felt after meals He continued to register pain until 75 cc of fluid had been withdrawn from the stomach, 100 cc of water was then injected into the stomach No pain followed

In all except one of our definite cases of ulcer pain has occurred either with gastric contractions or with high gastric acidity Case 4 is interesting as it shows that in certain persons pain can accompany both conditions Since no definite diagnosis was made, no conclusions can be drawn The man may have had neurasthenia and been more sensitive than the normal to visceral conditions

In 9 cases of epigastric pain with no demonstrable lesion of the stomach or duodenum, 6 of the patients reacted positively to the acid test Pain did not occur synchronously with gastric contractions in any of these cases

#### DIRECT APPLICATION OF ACID TO ULCER

Hydrochloric acid, in dilutions of 0.5 per cent, 1 per cent and 5 per cent was applied directly to the ulcer in 4 patients with gastric and duodenal ulcer during operation under local anesthesia No pain

response was elicited. The patients, however, responded with pain when the mesentery was pulled or when an unanesthetized area of the skin was pinched. Two of these patients gave positive results for acid in the Palmer test, and 2 gave definitely positive reactions to the motility test.

#### COMMENT

The striking division of our cases into those showing a positive pain response to acid but a negative motility response and into a second group showing a positive motility but a negative acid response is somewhat difficult to explain in view of some of the previous observations on the mechanism of pain in ulcer. Palmer and others have emphasized the importance of acid in the production of pain. He spoke of the condition necessary for the positive reaction to acid as "a sensi-

TABLE 3—*Results in Cases of Epigastric Pain Without Demonstrable Gastric or Duodenal Lesions*

Case	Condition	Acid Test		Motility Test	
		Number Positive	Number Negative	Number Positive	Number Negative
1	Disease of gallbladder		1		
2	Disease of gallbladder	1	1		1
3	Disease of gallbladder	2	1		2
4	Disease of gallbladder	2			1
5	Chronic appendicitis	1	1		1
6	Neurasthenia	5			3
7	Neurasthenia		2		
8	Neurasthenia		1		
9	Neurasthenia	2		2	

tivity of the pain-producing mechanism." He did not, however, define the factors of this pain sensitivity. He indicated that the quantity and the degree of acidity are important. Our observations on the direct application of acid to the ulcer would indicate that acid is not per se the important factor. Nor can increased general susceptibility to pain be a factor, for one of us has observed that patients with peptic ulcer, when subjected to tests for pain, respond in a normal or subnormal manner and are not hypersensitive. Konjetzny,<sup>13</sup> Faber<sup>14</sup> and others have called attention to the pyloric gastritis in gastric and duodenal ulcer. This gastritis occurs in the duodenum as well as in the antral portion of the stomach. The "sensitivity" to acid, using the expression of Palmer, we believe is due to the associated gastritis. This also offers a reasonable explanation for the recurrent periodic attacks of pain. Clinical observation recognizes the occurrence of gastritis of varying degree in cholecystitis and appendicitis. The positive acid response in

13 Konjetzny, G. E. Beitr. z. path. Anat. u. z. allg. Path. **71**: 595, 1923.

14 Faber, K. Chronic Gastritis in Relation to Asphyxia and Ulcer, *Lancet* **2**: 901, 1927.

these cases can readily be explained on the basis of sensitivity to acid because of the gastritis. The failure to obtain hunger contraction in these conditions is readily explained by the lack of tonus and contractions that invariably accompanies varying degrees of gastritis.

How shall we explain the group of gastric and duodenal ulcers that do not give a positive response to acid but are positive for gastric hunger contractions? One possibility is that mechanical obstruction, due to relative duodenal stenosis or duodenal narrowing, may intensify the hunger contractions. Although many of the cases at operation revealed varying degrees of duodenal narrowing with scar formation, it does not seem to us that this offers an explanation of pain synchronous with hunger contractions in all cases. Carlson has called attention to the fact that there are persons who respond definitely with painful sensations to normal hunger contractions, independent of any organic lesion in the stomach. These persons may be considered hypersensitive to the gastric motor mechanism. Is it not conceivable that in ulcer a similar condition may exist? We are still at a loss to explain the negative response to acid. Our observations on the stomach and duodenum of these patients also reveal a moderate degree of gastritis. It is conceivable that the sensitivity to acid is dependent on the varying degree of gastritis and that in the absence of this gastritis the dominating factor is not the acidity but gastric motility?

According to Hurst,<sup>15</sup> the only stimulus that causes any sensation in the stomach and intestine is tension—"slight tension, the sense of fullness, greater tension the sense of pain." He advocates the view that "acid acts indirectly by giving rise to a protective reflex, which results in achalasia of the pyloric sphincter." Achalasia and spasm of the pyloric sphincter only cause pain indirectly by preventing the relief of this tension in the pyloric vestibule, which the normal opening of the sphincter and the passage of chyme through the pyloric canal into the duodenum causes on the approach of each peristaltic wave. Our conception of the manner in which gastric motility produces pain in gastric and duodenal ulcer is one that is intimately associated with changes in the blood supply in and about the ulcerous area. Increased gastric contractions and gastric peristalsis we think are associated with depletion of the vascular bed in and about the ulcerous area, producing ischemia, asphyxia and resulting pain. In a previous communication (Meyer and Kartoon<sup>16</sup>) we advanced this hypothesis and suggested that the relief of pain on the intake of food, soda or spirits is intimately associated with improvement in the circulation of the stomach and

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15 Hurst, Arthur F., and Stewart, Matthew J. *Gastric and Duodenal Ulcer*, London, Oxford University Press, 1929, p. 159.

16 Meyer, Jacob, and Kartoon, Louis B. *Effect of Intravenous Injection of Foreign Protein on Peptic Ulcer*, *Arch Int Med* **46** 768 (Nov) 1930.

local vascular improvement about the ulcerous area. Increased peristalsis in hunger or at the end of a meal results in a depletion of the vascular bed in and about the ulcerous area, with resulting asphyxia, edema and pain. This hypothesis offers a reasonable explanation of the rhythmical character of the pain in ulcer which is entirely independent of acidity. It may likewise be the explanation of the paradoxical fact that acid, such as hydrochloric, or some other nutrient gives relief from pain in ulcer in some cases.

#### CONCLUSIONS

1 The results indicate that hydrochloric acid is not responsible for the pain in all cases of peptic ulcer.

2 As a result of experimental and clinical studies, we suggest that the pain in gastric ulcer is due to acid sensitivity when an associated gastritis is present. This same mechanism prevails in cholecystitis, appendicitis and probably colitis.

3 Pain in gastric and duodenal ulcer may be due to gastric hunger contractions and gastric motility.

4 The mechanism by which pain is produced by the hunger contractions and motility we believe is a depletion of the vascular bed in and about the ulcerous area resulting in asphyxia, edema and pain.

5 The positive acid response in cases without intrinsic gastric and duodenal lesions, as in disease of the gallbladder, chronic appendicitis and gastric neurosis, would indicate the unreliability of "the acid test" for gastric and duodenal ulcer.



## Book Reviews

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**The Action of Muscles Including Muscle Rest and Muscle Re-Education**  
By Sir Colin Mackenzie, M D, F R C S, F R S (Edin), Professor of Comparative Anatomy and Director of the Australian Institute of Anatomy, Canberra, formerly member of the Council of the Anatomical Society of Great Britain and Ireland, and of the Staff of the Military Orthopaedic Hospital, Shepherd's Bush, London, and Examiner in Anatomy to the Universities of Melbourne and Adelaide, Co-Editor of "Treves' Surgical Anatomy" Second edition Price, \$3 50 Pp 288, with 100 illustrations New York Paul B Hoeber, Inc, 1930

At the February meeting of the Congress on Medical Education, Medical Licensure and Hospitals, one session (on February 16) was devoted to physical therapy. This evidence of the increasing importance attached by the medical profession to this subject explains somewhat the demand for a second edition of this book, for, as Mackenzie says, physical therapy is myology, and it is only "a question of time when a Department of Myology will be a principal feature in every orthopedic institution." Muscles constitute more than 40 per cent of the weight of the ordinary man, treatment of their disabilities furnishes most of the work of the physical therapists, and a better understanding of their mode of action has already led to great improvement in treatment, in reeducation of muscles and in the after-lives of patients, especially of those disabled by poliomyelitis or wounds sustained at war. The results obtained by Mackenzie and others are so surprisingly good that study of the subject becomes an urgent obligation of the medical profession.

The first part of the book deals with general principles, the second and larger part, with particular muscles. Among the principles, some that are emphasized especially are

- 1 The part actually played by a muscle is not easy to detect. It cannot be predicted *a priori*. It must be studied in action on the living body. The skill of palpating fingers is the only reliable guide.

- 2 Muscles act individually as units, one part cannot have an action opposing that of another part.

- 3 Each has an antagonist. Voluntary stimulation of a prime mover effects the relaxation of the antagonist. Such relaxation is a guide to determining the real function of prime movers. Judged by this criterion, the brachialis is the real flexor of the forearm and not the biceps, since stimulation of the brachial only is accompanied by relaxation of the triceps.

- 4 Absolute rest is essential in treatment. The notion that massage is necessary to preserve a muscle temporarily paralyzed is quite wrong.

- 5 The only real test for muscle recovery is scientifically directed volitional movement.

- 6 Muscles have several separate functions acquired serially in the course of evolution. The loss of function and its recovery follow in the patient the same order as did the development in evolution.

Whether one agrees with Mackenzie's statement of all these principles or not, the interest and therapeutic importance of them are obvious. The practical physician and nurse will be interested in comparing the statement of the actions of specific muscles with those made by other workers, especially with those of Miss Wright in this country. For the most part, they agree, sometimes, as in the case of the biceps brachii, they do not agree perfectly. In these instances, Miss Wright's statement seems to be in accord with the actual working of these muscles, as observed by the reviewer.

An especial feature of this book lies in the understanding and practical application of the evolutionary history of muscles, for they lose their actions and reacquire them in an order that is in strict accord with their progressive evolution. Few authors have ever brought to the consideration of muscle action in man so thorough an understanding of comparative anatomy and evolution.

The second edition contains a new section on the evolutionary role of muscles in the development and maintenance of the erect posture characteristic of man.

The book is both scientific and practical. It deals at an opportune time with an interesting and important subject. It cannot fail to be of great interest to all who seek to understand the action of muscles and to treat their disabilities. The application of some of the principles, not generally recognized, which are set forth clearly and convincingly, should result in saner treatment and much more complete restoration of function than has been expected hitherto even more than was thought possible by most workers.

**Die Dickdarmschleimhaut, ihre normale und pathologische Funktion im Röntgenbilde** By Dr. Werner Knothe. Price, 8 marks. Pp. 53, with 113 illustrations. Leipzig: Georg Thieme, 1932.

In this monograph the author has attempted to show the value of the roentgenologic "relief picture" of the colonic mucosa.

The technic for the preparation of the patient for study of the colon is described. The bowel should be entirely empty. This is accomplished by giving enemas several times during the two days preceding the examination. As contrast material the author uses a mixture of three parts of barium sulphate prepared for x-ray work and seven parts of water. The contrast enema is given under fluoroscopic control with the patient in the prone position. The detail studies are made after the bowel has been emptied as completely as possible, the mucosa being covered with only a thin film of the contrast material.

After a short discussion of the anatomy and physiology of the normal colon, the roentgenographic appearance is described and illustrated. Three types are distinguished, namely, the quietly segmenting, the actively segmenting and the contracting. In all of these the folds of mucosa are quite uniform.

The greater portion of the first half of the monograph is devoted to manifestations of functional disturbances of the colon. In the author's opinion these findings are brought about through vagus irritation. They represent a state of spasm of the mucosa associated with a spasm of the muscularis propria. This leads to a disordered formation of folds even though there are no evidences of inflammation or other anatomic changes in the bowel. To prove this point he has studied the effect of cold enemas, pilocarpine and atropine on the colon. The first two definitely stimulated the bowel, throwing the mucosa into an increased number of irregular folds. Atropine relaxed the bowel after stimulation by cold or pilocarpine. These effects are illustrated.

The second half of the monograph deals with pathologico-anatomic changes of the colon. The development of nonspecific ulcerative colitis is divided into three stages each of which may be distinguished roentgenologically. The first or acute stage is characterized by broad areas of swelling, ulceration and undermining of the mucosa. In the second stage the ulceration and undermining disappear and the swelling subsides considerably. This suggests that healing is taking place, and in most cases the process does not extend beyond this stage. The characteristic of the third stage is its rather finely granular appearance without evidence of swelling. Very little is said about the roentgen findings in tuberculosis of the colon because the author states that this subject will be dealt with at another time. It is stated that appendical disease may result in cecal irritability. Diverticula of the colon produce irritation or partial obstruction only when secondary infection is present. No evidence of carcinomatous degeneration in diverticulosis was seen in the forty cases studied. Finally there is a short discus-

sion on changes in the relief picture by a neoplasm. Here also signs of irritability of the colon develop only after there is secondary infection of the lesion.

This monograph is highly recommended to those interested in diseases and disturbances of the colon. Its chief value lies in the numerous and exceptionally good illustrations. The text is primarily devoted to their explanation.

**Herz und Angst** By Professor Ludwig Braun. Price, 6 marks. Pp 119. Vienna: Franz Deuticke, 1932.

New points of view are likely to be stimulating and provocative. Such, indeed, describes the reviewer's reaction to the monograph of Professor Braun. The main line of argument relative to the important place that the symptom "Angst" takes in the clinical picture of cardiac disease is instructive and well repays the interest of the reader. The usual physical phenomena of cardiac disease are not emphasized. There are no description of pathology, little mention of standard methods of diagnosis and almost no mention of medical treatment. The monograph is devoted to the psychologic and emotional aspects of cardiac disease, especially as they are manifested in patients with the anginal syndrome. The discussion turns largely about the meaning of the word "Angst" its derivation, its development through various literatures and its significance to the physician at the bedside in the presence of the patient, whose outlook on life has been abruptly and fundamentally altered. Differing from fear in that it has nothing outside itself of which to be afraid, "Angst" appears where life is endangered as a "protective reaction in the lower, a conscious sensation in the higher organism." It is the constricting tightening, crushing sensation, indescribable, unbearable and dreadful, which, once experienced, changes the entire emotional outlook of its victims. "The specific sensation of the heart, its psychic signature, its speech, is the "Angst-empfindung."

This description of the emotional and psychologic status of the patient who has once endured the "Angst" of cardiac disease is calculated to widen the mental horizon of the practitioner, to give him a far better insight into the mind and character of the patient with angina than he has thought of before. On the other hand, the chapter on the "Diagnostic Significance of the Angsttraumes" so permeated with Freudian psychology, carries little conviction, especially to one unschooled in this system of psychology.

A final chapter on euthanasia is unrelated to the main theme of the book. As the title implies, this chapter is devoted to a discussion of a subject that may be academically plausible, but practically is far short of justifiable. Few are the physicians who wish to add to the power already possessed to relieve pain, the responsibility inevitably attendant on the right to end it.

**Psychology and Psychiatry in Pediatrics: The Problem** Subcommittee on Psychology and Psychiatry, White House Conference on Child Health and Protection. Bronson Crothers, M.D., Chairman. Price, \$1.50. Pp 146. New York: Century Company, 1932.

The main thesis defended in this report is that adequate medical care of the child cannot be given without intelligent attention to any intellectual and emotional difficulties that may be present. Physicians are warned that unwillingness on their part to acquire the ability to deal wisely with problems involving the personality of the child may lead to transfer of this field to formal organizations or to persons without medical experience, which will diminish the prestige of the medical practitioner. There are extracts of discussions by Esther Loring Richards, Borden S. Veeder, Adolf Meyer, Douglas Thom and others. The workings of a typical child guidance institute are described in detail.

## UREA CLEARANCE TEST AS AN INDEX OF RENAL FUNCTION

### I STUDIES OF NORMAL SUBJECTS

MAURICE BRUGER, M D \*

AND

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In 1921, Austin, Stillman and Van Slyke,<sup>1</sup> while developing the urea secretory constant, discovered two laws of urea excretion. They found that the normal rate of urea excretion in man and dog increases, first, in direct proportion to the blood urea concentration, and second, in proportion to the square root of the urinary volume per unit of body weight. They also showed that a rising volume of urine is not indefinitely accompanied by an increase in the output of urea. The point at which an acceleration of the urinary flow is not paralleled by further elimination of urea they termed the "augmentation limit," and placed it between 2.5 and 6 liters of urine per twenty-four hours in normal persons, that is, from 1.7 to 4.1 cc per minute.

These original concepts were verified in 1928 by Moller, McIntosh and Van Slyke,<sup>2</sup> who in a study of seven normal persons found that the "augmentation limit" was between 1.67 and 2.55 cc of urine output per minute. The amount of blood cleared of urea in one minute under these conditions of urinary activity they termed the maximum urea clearance ( $C_m$ ). They found this to average about 75 cc of blood in normal persons. In other words, efficient kidneys excreting urine at any rate above 2 cc per minute can clear about 75 cc of blood of its urea in one minute. This figure can be calculated from the urea concentrations in the blood and urine ( $B$  and  $U$ , respectively) and the urine output in cubic centimeters per minute ( $V$ ) as follows:

$$\text{Maximum clearance } (C_m) = \frac{UV}{B}$$

For volumes of urine of less than 2 cc per minute, Moller, McIntosh and Van Slyke<sup>2</sup> calculated the standard clearance ( $C_s$ ), which repre-

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1 Austin, J. H., Stillman, E., and Van Slyke, D. D. Factors Governing the Excretion Rate of Urea, *J. Biol. Chem.* **46**: 91, 1921.

2 Moller, E., McIntosh, J. F., and Van Slyke, D. D. Studies of Urea Excretion. II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, *J. Clin. Investigation* **6**: 427, 1928.

sents the amount of blood cleared of its urea when the urine volume is at the average level of 1 cc per minute. They found this to average about 54 cc of blood, that is, normal kidneys excreting urine at the average rate of 1 cc per minute can clear about 54 cc of blood of its urea in one minute. This figure can be calculated as follows,  $U$ ,  $B$  and  $V$  denoting the same elements as in the foregoing equation

$$\text{Standard clearance } (C_s) = \frac{U\sqrt{V}}{B}$$

Taylor, Drury and Addis<sup>3</sup> have shown that the urea excretion ratio of Addis,<sup>4</sup> which is analogous to the maximum urea clearance, varies with the surface area of the body more than it does with the weight. In a second paper, McIntosh, Moller and Van Slyke<sup>5</sup> verified this for the urea clearance, and found that more constant normal values can be obtained if the volume of urine excreted by the subject is corrected for surface area. In a recent paper, Ralli, Brown and Pariente<sup>6</sup> have shown that the determination of the standard clearance in normal dogs gives more uniform results if the amount of blood cleared of its urea is determined for a unit of surface area of the body. Basing their calculations on medico-actuarial tables, Van Slyke<sup>5</sup> and his co-workers have adopted 1.73 square meters as the average surface area. The corrected volume of urine output is determined as follows

$$V_c = V \times \frac{1.73}{SA}$$

$V$  equals the observed excretion of urine per minute in cubic centimeters and  $SA$  equals the surface area of the body.

The present report is based on a study of the urea clearance in normal human subjects. All collections of urine and blood were made by one of us personally. The persons investigated were studied for at least two successive hours on the same day, and the average clearance was determined. In all cases the urine volumes were corrected for surface area.

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3 Taylor, F. B., Drury, D. R., and Addis, T. The Regulation of Renal Activity. VIII. The Relation Between the Rate of Urea Excretion and the Size of the Kidneys, *Am J Physiol* **65** 55, 1923.

4 Addis, T., and Watanabe, C. K. A Method for the Measurement of the Urea Excreting Function of the Kidney, *J Biol Chem* **28** 251, 1916. Addis, T. Renal Function and the Amount of Functioning Tissue, *Arch Int Med* **30** 378 (Sept) 1922.

5 McIntosh, J. F., Moller, E., and Van Slyke, D. D. Studies of Urea Excretion. III. The Influence of Body Size on Urea Output, *J Clin Investigation* **6** 467, 1928.

6 Ralli, E. P., Brown, M., and Pariente, A. The Urea Clearance Test in Normal Dogs, *Am J Physiol* **97** 432, 1931.

## PROCEDURE

The procedure suggested by Moller, McIntosh and Van Slyke<sup>2</sup> was used throughout these studies. Breakfast was allowed but coffee was withheld, since Addis and Drury<sup>7</sup> have shown that coffee increases the urea clearance. The subjects, however, were not put to bed, but performed their usual laboratory, clerical or hospital duties. This was done because we wished to investigate the effect of moderate exercise on the blood urea clearance and thus determine the possibility of applying the urea clearance test to patients seen and studied in a physician's office or a hospital dispensary.

The test was carried out as follows (all steps were timed to the fraction of a minute)

9 00 a m	Bladder emptied, urine discarded
10 00 a m	Bladder emptied, urine volume measured, urea nitrogen determined
10 05 a m	Sample of blood obtained by venous puncture, urea nitrogen determined
11 00 a m	Bladder emptied, urine volume measured, urea nitrogen determined

The height and weight were then determined.

In some instances the urea clearance was studied for four consecutive hours, when the test was thus prolonged another specimen of blood was obtained two hours after the first, and the urea content of this second blood sample was used to calculate the clearances for the last two hours.

In every case the procedure was carried out in the morning, since MacKay<sup>8</sup> has shown that urea excretion is least liable to marked fluctuation in the morning hours.

The urea nitrogen in the blood and in the urine was determined by the gasometric urease method of Van Slyke<sup>9</sup>.

Urine volumes were always corrected for surface area, DuBois tables being used. The standard adopted for body area was 1.73 square meters. For urine rates less than 2 cc per minute, the standard clearance was determined by the following formula

$$C_s = \frac{U \sqrt{V_c}}{B}$$

$U$  equals the urine urea nitrogen in milligrams per hundred cubic centimeters.  $B$  equals the blood urea nitrogen in milligrams per hundred cubic centimeters and  $V_c$  equals the amount of urine (in cubic centimeters) per minute  $\times \frac{1.73}{\text{surface area of subject}}$ .

For rates of urine flow above 2 cc per minute, the maximum clearance was determined according to the formula

$$C_m = \frac{U V_c}{B}$$

$U$ ,  $B$  and  $V_c$  denote the same elements as in the foregoing equation.

7 Addis, T, and Drury, D. R. The Rate of Urea Excretion. VII. The Effect of Various Other Factors than Blood Urea Concentration on the Rate of Urea Excretion, *J. Biol. Chem.* **55** 629, 1923.

8 MacKay, E. M. Studies of Urea Excretion. V. The Diurnal Variation of Urea Excretion in Normal Individuals and Patients with Bright's Disease, *J. Clin. Investigation* **6** 505, 1928.

9 Van Slyke, D. D. Determination of Urea by Gasometric Measurement of Carbon Dioxide Formed by the Action of Urease, *J. Biol. Chem.* **73** 695, 1927.



## RESULTS

Thirty hours of observation was carried out on eight normal subjects. The results are given in tables 1 and 2. The average standard clearances varied from 55.5 to 82.2 cc of blood. The mean for the whole group was 69.6 cc. In a study of their own normal values and those calculated from data in the literature, a total of one hundred and eight hours of observation on eighteen normal subjects, Moller, McIntosh and Van Slyke<sup>2</sup> noted variations in the standard clearances of from 40.1 to 68.3 cc of blood with a mean of 54.5 cc.

Addis and Drury<sup>7</sup> and Mackay<sup>8</sup> have shown that strenuous and prolonged exercise, such as running for one hour or playing several sets of tennis, diminishes the blood urea clearance. MacKay assumed that hard exercise probably increases the blood flow to muscular tissues, resulting in a diminution in the renal circulation. In our studies, however, the subjects carried out their routine duties which did not entail severe exertion. The average amount of blood cleared of urea per unit of time in our cases was distinctly higher than that recorded by Moller, McIntosh and Van Slyke,<sup>2</sup> who kept their subjects in bed. The maximum deviation from the mean of the group in both series, however, was the same, namely  $\pm 13$  cc. We can assume, therefore, that the very moderate exercise allowed our subjects raised the blood urea clearance, possibly owing to an increased renal circulation.

At first we believed that this finding would require an alteration of the normal standard in the calculation of renal function as a percentage of the normal value for cases of Bright's disease seen and studied in a hospital dispensary or in a physician's office, since such patients make a certain amount of physical effort to reach the physician. It soon became apparent, however, as will be seen later, that when renal impairment exists, the kidney is far from labile, and moderate exercise is without influence on the blood urea clearance.

## COMMENT

In this and in subsequent papers, we have expressed the urea clearance as a percentage of the normal value, using Van Slyke's figures of 54 cc of blood for the normal average standard clearance and 75 cc for the normal average maximum clearance. That is, if a person has a standard clearance of 54 cc of blood, he is considered to have 100 per cent of urea clearance. If he has a standard clearance of 27 cc of blood, his urea clearance is only 50 per cent of normal and so on. The percentage of normal clearance can readily be obtained by multiplying the standard and maximum clearances by the factors 1.85 and 1.33, respectively.



A study of the protocols of Van Slyke and his collaborators and of our own makes it apparent that the percentage of urea clearance varies markedly in a normal person. Within three hours a subject may show a variation of from 132 to 73 per cent in the urea clearance (A J M, 7, table 1). In the same subject, studied on different days, the urea clearance may vary between 204 and 104 per cent (H D, 3 and 10, table 1). On the whole, the variations recorded by us are no greater than those observed by Van Slyke and his associates.

It may be mentioned here that as the urea clearance diminishes, with impaired renal function, it shows fewer variations and becomes more and more fixed, resembling in this respect the specific gravity of the urine. The normal kidney, however, is extremely labile, its functional elasticity is indicative of its normality. Unlike the diseased organ, the normal kidney responds by increased or decreased activity to moderate exercise, to severe exertion, to drugs, to various kinds of food and in all probability to many other factors.

We cannot conceive that the urea clearance could be fixed in normal persons irrespective of any attempts to standardize the conditions of the test. The glomeruli in the normal kidney, as Wearn and Richards<sup>10</sup> have shown, function intermittently, and according to the prevailing diuretic stimuli only a few or a great many may be active, there may be a large amount of blood flowing through the glomeruli or none at all, the intraglomerular blood pressure varies a great deal, the nerve fibers that exist between the tubules and in the glomerular tuft indicate a nervous control of renal activity. For these reasons and many others, it may be safely concluded that the normal kidney has enormous reserve power and varies its pace accordingly. We stress this point because the figure 100 per cent, or any other per cent, of urea clearance is relative to many controlled and uncontrolled, and many known and unknown, factors, at least in normal subjects. The absolute value of the kidney function of any normal person is not determined by the present test or by any other. Of far greater significance as a measure of renal efficiency is the degree of variation in the functional capacity of the kidney, which reflects renal effort and reserve. The urea clearance, like the specific gravity of the urine, when studied in normal subjects bears out this point well.

We shall have occasion to show that the figures for urea clearance are of clinical value, but they should not be interpreted dogmatically as absolute values of renal function. Fifty per cent of average normal urea clearance does not have the same relative significance, nor does it

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<sup>10</sup> Wearn, J. F., and Richards, A. N. Observations on the Composition of Glomerular Urine with Particular Reference to the Problem of Reabsorption in the Renal Tubules, *Am J Physiol* **71** 209, 1924.

ment the same evaluation as, for instance, a hemoglobin reading. Normal subjects are known to have given values of 52 per cent (Van Slyke) and 58 per cent <sup>11</sup> on single observations. Of far greater importance are clearance values repeatedly and consistently low, reflecting fixation of renal effort, which is characteristic of kidney impairment.

#### SUMMARY

Thirty hours of clearance studies in eight normal subjects under moderate exertion are reported. A comparison of our data with those published by Moller, McIntosh and Van Slyke <sup>2</sup> shows that moderate exercise definitely increases the blood urea clearance of normal persons, compared to that of persons lying down throughout the test.

The blood urea clearance varies a great deal in normal persons. A fixation of the clearance values at a low level is necessary to establish the existence of an impairment of kidney function. A single determination as low as 52 per cent of normal is not necessarily an indication of diminished renal activity.

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<sup>11</sup> Bruger, M., and Mosenthal, Herman O. Urea Clearance Test as an Index of Renal Function. II. The Effect of Ingestion of Carbohydrate (Dextrose), *Arch Int Med*, this issue, p. 358.

# UREA CLEARANCE TEST AS AN INDEX OF RENAL FUNCTION

## II THE EFFECT OF INGESTION OF CARBOHYDRATE (DEXTROSE)

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AND

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The influence on the blood urea clearance of the ingestion of carbohydrate in the form of dextrose was studied in six persons. The subjects were normal, except that they were reported to have exhibited glycosuria at some previous time. The sugar tolerance test showed that, in regard to their carbohydrate metabolism, three of the subjects were normal, two showed a diminished tolerance for carbohydrates and one had renal glycosuria. None of these disturbances should influence the function of the kidney, as far as the elimination of urea is concerned. By timing carefully the taking of the specimens of urine and blood, we were able to study the blood urea clearance over shorter and longer periods before and after the ingestion of 100 Gm of dextrose (table 1).

### PROCEDURE

The urea clearance tests were carried out in the same fashion as those described in the preceding paper of this series,<sup>1</sup> except that the time intervals were varied somewhat, and that 100 Gm of dextrose was administered after the first timed specimen of urine had been obtained. The details of these variations are made clear in table 1.

The subjects investigated were not kept in bed but, except for maintaining the sitting posture, were at complete rest in the intervals between the taking of the specimens of blood and of urine. The conditions, therefore, approached more closely those of Moller, McIntosh and Van Slyke<sup>2</sup> than those described in the preceding paper.

### RESULTS

Twenty-eight observations were carried out on six subjects. The results are given in tables 1 and 2. The average standard clearances

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\* Oliver Rea Fellow in Medicine.

1 Brugger, M., and Mosenthal, H. O. Urea Clearance Test as an Index of Renal Function. I. Studies of Normal Subjects, *Arch Int Med*, this issue, p 351.

2 Moller, E., McIntosh, E. F., and Van Slyke, D. D. Studies of Urea Excretion. II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, *J Clin Investigation* 6 427, 1928.

TABLE 1—*Effect of Ingestion of Dextrose on the Urea Clearance*

Subject	Time of Collection of Urine	V	V <sub>c</sub>	U	B	Maximum Clearance Calculated for Urine Volumes Above 2 Cc per Minute	Standard Clearance Calculated for Urine Volumes Below 2 Cc per Minute	Percentage of Normal Calculated on Basis of Cs = 54 Cm = 75	Comment
		Urine Volume, Cc per Minute	Urine Volume Corrected for Surface Area, Cc per Minute	Urine Urea Nitrogen, Mg per 100 Cc	Blood Urea Nitrogen, Mg per 100 Cc				
1 J M H	7 55 - 9 24½	1 16	0 90	831 0	9 67		81 6	150 9	100 Gm dextrose at 9 25 Diminished sugar tolerance
	9 24½- 9 48	0 72	0 56	783 6	10 03		58 5	108 3	
	9 48 -10 08½	0 53	0 42	886 6	9 79		58 4	108 1	
	10 08½-10 29	0 61	0 47	1309 8	9 42		95 5	176 8	
	10 29 -11 29	0 70	0 54	1132 5	8 70		95 8	177 3	
	11 29 -12 28½	0 58	0 45	932 9	7 62		82 0	151 8	
2 M O	7 22 - 9 22	0 64		1271 2	15 44		60 0	111 2	100 Gm dextrose at 9 22
	9 22 -10 03	0 67		1414 4	15 34		68 1	126 2	
	10 03 -10 26½	0 89		1345 9	14 24		80 2	148 6	Normal sugar curve
	10 26½-10 50	3 89		384 2	15 18	81 3		108 4	
	10 50 -11 53	8 01		149 7	14 91	66 5		88 6	
	11 53 -12 41	9 89		126 1	13 91	74 0		98 7	
3 F J O	8 30 -10 03	0 65		547 6	8 24		53 6	99 1	100 Gm dextrose at 10 03
	10 03 -11 11½	1 26		406 5	8 67		52 6	97 3	
	11 11½-12 09	1 05		430 5	9 07		48 6	89 9	Diminished sugar tolerance
4 J A H	7 20 -10 01	0 99	0 86	500 5	9 05		50 9	94 1	100 Gm dextrose at 10 01
	10 01 -10 37	1 59	1 37	486 0	9 13		62 3	115 2	
	10 37 -11 08	0 71	0 61	578 3	9 44		47 8	88 4	Renal glycosuria Normal sugar curve
	11 08 -12 05	3 31	2 88	278 7	8 72	92 0		122 4	
	12 05 - 1 18½	0 16	0 14	733 7	8 69		31 2	57 8	
5 M Ba	7 45 - 9 37	0 82		534 1	7 14		67 8	125 4	100 Gm dextrose at 9 37
	9 37 -10 05	1 77		354 9	7 29		64 7	119 7	
	10 05 -10 30	4 72		121 1	7 07	80 9		107 5	Normal sugar curve
	10 30 -10 46	1 13		410 7	7 53		57 8	107 0	
	11 47 -12 47	3 33		169 3	5 04	112 0		148 9	
6 M K	9 45 -10 13½	2 02		425 9	10 64	80 7		107 6	100 Gm dextrose at 10 14
	10 13½-11 25	1 48		530 4	9 93		64 6	119 6	
	11 25 -12 26½	1 11		705 2	10 14		73 1	135 2	Normal sugar curve

TABLE 2—*Summary*

Subject	Number of Observations	Standard Clearance			Maximum Clearance			Percentage of Normal Calculated on Basis of Cs = 54    Cm = 75		
		Average	Maximum	Minimum	Average	Maximum	Minimum	Average	Maximum	Minimum
J M H	6	78 6	95 8	58 4				145 5	177 3	108 1
M O	6	69 4	80 2	60 0	73 9	81 3	66 5	113 6	148 6	88 6
F J O	3	51 6	53 6	48 6				95 4	99 1	89 9
J A H	5	48 1	62 3	31 2	92 0			95 6	122 4	57 8
M Ba	5	63 4	67 8	57 8	96 5	112 0	80 9	121 7	148 9	107 0
M K	3	68 9	73 1	64 6	80 7			120 8	135 2	107 6
Mean		63 3			85 8					
Maximum		78 6			96 5					
Minimum		48 1			73 9					
Maximum observed deviation of an individual mean from mean of group		±15			±11					

varied between 481 and 786 cc of blood with a mean of 633 cc. The average maximum clearances varied between 73.9 and 96.5 cc with a mean of 85.8 cc. A comparison of the foregoing standard clearances with those recorded in the preceding paper<sup>1</sup> shows that the ingestion of dextrose has little effect on the blood urea clearance. This is in full accord with the observations of Addis and Drury,<sup>3</sup> who studied the effect of the ingestion of 50 Gm of cane sugar on the urea excretion ratio of Addis,<sup>4</sup> which, as has been mentioned before, is identical with the maximum urea clearance. The average standard clearance is only slightly lower than that in our first series, this is probably due to the subjects' maintenance of the sitting posture. A comparison of the present figures with those of the preceding paper and with those of Moller, McIntosh and Van Slyke<sup>2</sup> shows that the approximately identical percentage of increase in both our average standard and our maximum clearance is probably due to nothing more than our deviation from conditions of absolute rest and not to the effects of the ingestion of dextrose.

In three of our subjects definite diuresis followed the ingestion of the dextrose. In one of these (J. A. H., 4, table 1) the increased output of urine was associated with an increase in the blood urea clearance, but this was not observed in the other two. In fact, one subject (M. O. 2, table 1) tended to show a decrease in the maximum urea clearance with increased flow of urine. Bourquin and Laughton<sup>5</sup> have shown that in dogs diuresis is first associated with an increased urea clearance and that, as the diuresis subsides, the clearance falls. Bruger and Stehle<sup>6</sup> observed during the diuresis resulting from the intravenous injection of 260 cc of isotonic dextrose into dogs with fistula of the bladder, that the volume of output of urine varies more or less inversely with the urea concentration in the urine. It is impossible to determine the urea clearances from these authors' protocols, since the urea content of the blood was not determined. Assuming a constant blood urea content, their results tend to show an increase in the clearance as the diuresis advances and a fall as the output of urine diminishes. Moller, McIntosh and Van Slyke<sup>2</sup> were unable

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3 Addis, T., and Drury, D. R. The Rate of Urea Excretion. VII. The Effect of Various Other Factors than Blood Urea Concentration on the Rate of Urea Excretion, *J. Biol. Chem.* **55**: 629, 1923.

4 Addis, T. Renal Function and the Amount of Functioning Tissue, *Arch. Int. Med.* **30**: 378 (Sept.) 1922.

5 Bourquin, H., and Laughton, N. B. Factors Influencing the Excretion of Urea. II. Diuresis and Caffeine, *Am. J. Physiol.* **74**: 436, 1925.

6 Bruger, M., and Stehle, R. L. The Effect of Solutions of Dextrose and Various Electrolytes, Intravenously Administered, on the Rate of Secretion and Composition of the Urine, unpublished data.

to verify this in human subjects. In the few cases in which we observed any diuresis following the ingestion of dextrose there was no constant relationship between diuresis and urea clearance. Assuming that diuresis affects the urea clearance, we should expect to find larger deviations of the average clearances from the mean of the group than in cases without any diuretic response, but this was not observed.

#### COMMENT

In the present series the same wide variations of the urea clearance values are evident as were observed in the persons reported on in the first paper<sup>1</sup>. One case (J A H, 4, table 1) is especially noteworthy. The clearance, expressed as a percentage of the normal value, varied between 122 and 58 per cent within two hours. In other words, the ability of the kidney to eliminate urea was more than twice as effective in one hour than it was in the following hour. As was stressed in the previous paper, this is typical of the normal kidney.

On purely physiologic grounds it is conceivable that diuresis may result in an increased excretion of urea per unit of time followed by a diminished output as the diuresis subsides. Urea, as a nonthreshold body, can be subjected to a "washing out" process. As was mentioned, the results of Bouiquin and Laughton<sup>5</sup> and of Biuger and Stehle<sup>6</sup> in dogs suggest this. On the other hand, no constant relationship between diuresis and urea clearance has been observed in human subjects. It is probable that the degree of diuresis observed by Van Slyke and his associates and by ourselves in normal persons is not great enough or sufficiently prolonged to affect appreciably the absolute urea content of the body.

#### SUMMARY

Twenty-eight observations of the urea clearance in six subjects with normal kidneys before and after the ingestion of 100 Gm of dextrose are reported. The ingestion of dextrose has little or no effect on the blood urea clearance. The degree of diuresis following the ingestion of dextrose in human subjects has little effect on the blood urea clearance.

# DIETARY PRACTICES IN RELATION TO THE INCIDENCE OF PELLAGRA

I A STUDY OF FAMILY DIETARIES IN LEON COUNTY, FLORIDA

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The importance of diet in the prevention and treatment of pellagra is generally accepted. It is not yet clear, however, whether we are dealing with a specific dietary deficiency or whether the deficiency is of a more general nature, important primarily in lowering the body's resistance to disease. Medical opinion in the South is still divided, though the weight of evidence at present available supports the conception of a specific deficiency.

This confusion in our ideas of the relation of diet to the disease is a natural one, in view of the number of theories that have been advanced to explain the relationship. The "spoiled corn" theory, though developed in Italy, was advocated in this country<sup>1</sup> after the recognition of the disease here. While American investigators found no evidence of a specific relation of corn to the incidence of the disease, emphasis on this theory served to confuse the issue and to divert attention from the consideration of other factors in the diet.

The points receiving emphasis during the decade 1910 to 1920 are perhaps illustrated in the work of Siler, Garrison and MacNeal,<sup>2</sup> who studied such problems as the influence of (a) cornmeal, homegrown or shipped, sound or decayed, (b) the possible injurious effect of the use of canned foods and (c) the use of animal protein foods, such as meat, milk and eggs. With emphasis in their studies placed on the possible deleterious effect of the use of cornmeal or canned foods, it is not surprising that they minimized the positive influence of milk which they found, and concluded that diet was less important than domiciliary relationship.

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From the School of Home Economics, Florida State College for Women

1 Marie, A. Pellagra, translated from the French by C. H. Lavinder and J. W. Babcock, Columbia, S. C., The State Company, 1910. Harris, H. F. Pellagra, New York, The Macmillan Company, 1919.

2 Siler, J. F., Garrison, P. E., and MacNeal, W. J. A Statistical Study of the Relation of Pellagra to the Use of Certain Foods and to the Location of Domicile in Six Selected Industrial Communities, Arch Int Med **14** 293 (Sept.) 1914.

Voegtlin<sup>3</sup> and Goldberger and his associates<sup>4</sup> in the Public Health Service were convinced that diet stood in causal relation to pellagra, but their first experiments, in which they used a liberal mixed diet for prevention or cure, offered no conclusive evidence of a specific deficiency. They<sup>5</sup> suggested the possibility of a protein (or perhaps amino-acid) deficiency, a theory not accepted by all students of the disease, but on which attention was centered for some time. Bigland<sup>6</sup> and Boyd and McLean<sup>7</sup> emphasized the "biological value" of the protein of their diets, almost to the exclusion of other dietary factors, and Jobling and Peterson<sup>8</sup> analyzed their findings in terms of protein requirements, total protein and sources of protein in the diet.

The institutional studies of Goldberger and his co-workers<sup>9</sup> were the first to show under controlled conditions the value of individual food materials in the prevention and cure of pellagra. As, however, the difficulty of work with human subjects has made progress in this direction slow, the production in experimental animals of symptoms which these authors<sup>10</sup> considered analogous to pellagra in human beings

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3 Voegtlin, C. Recent Work on Pellagra, in the Harvey Lectures, ser 15, Philadelphia, J. B. Lippincott Company, 1920.

4 Goldberger, J., Waring, C. H., and Willets, D. G. Treatment and Prevention of Pellagra, U. S. Pub. Health Rep. **29** 2821, 1914, Prevention of Pellagra. A Test of Diet Among Institutional Inmates, *ibid* **30** 3117, 1915.

5 Goldberger, J., and Tanner, W. F. Amino-Acid Deficiency Probably the Primary Etiological Factor in Pellagra, U. S. Pub. Health Rep. **37** 462 (March 3) 1922. Goldberger, Waring and Willets (footnote 4, second reference).

6 Bigland, A. D. Pellagra Outbreak in Egypt, Pellagra Among Ottoman Prisoners of War, *Lancet* **1** 947, 1920.

7 Boyd, F. D., and McLean, B. S. Report of Committee of Inquiry Regarding Prevalence of Pellagra Among Turkish Prisoners of War, *J. Roy. Army M. Corps* **33** 426 and 508, 1919, *ibid* **34** 70, 173 and 272, 1920.

8 Jobling, J. W., and Peterson, W. J. The Epidemiology of Pellagra in Nashville, Tennessee, *J. Infect. Dis.* **18** 501 (Jan.) 1916, Epidemiology of Pellagra in Nashville, Tennessee. II, *ibid* **21** 109 (Aug.) 1917.

9 Goldberger, J., and Tanner, W. F. Study of Treatment and Prevention of Pellagra, U. S. Pub. Health Rep. **39** 87 (Jan. 18) 1924, A Study of the Pellagra-Preventive Action of Dried Beans, Casein, Dried Milk and Brewer's Yeast, with a Consideration of the Essential Preventive Factors Involved, *ibid* **40** 54 (Jan. 9) 1925. Goldberger, J., Wheeler, G. A., Lillie, R. D., and Rogers, L. M. Further Study of Butter, Fresh Beef and Yeast as Pellagra Preventives, *ibid* **41** 297 (Feb. 19) 1926, Goldberger, J., and Wheeler, G. A. Study of Pellagra Preventive Action of Tomato, Carrot and Rutabaga Turnip, *ibid* **42** 1299 (May 13) 1927, Pellagra Preventive Action of Cowpea and Commercial Wheat Germ, *ibid* **42** 39, 2383 (Sept. 30) 1927.

10 Goldberger, J., Wheeler, G. A., Lillie, R. D., and Rogers, L. M. Study of Black-Tongue Preventive Action of Sixteen Foodstuffs, with Special Reference to the Identity of Black-Tongue in Dogs and Pellagra of Man, U. S. Pub. Health Rep. **43** 1385 (June 8) 1928.



opens up a fertile field for investigation, with promise of more rapid progress in solution of the problems concerned

During the last few years, there have been reported a number of cases of pellagra following restrictions in the diet Carley<sup>11</sup> reported a case of voluntary restriction resulting in the appearance of symptoms of pellagra which cleared up when a liberal mixed diet was prescribed Eusterman and O'Leary<sup>12</sup> reported 13 cases of the disease secondary to some interference with nutrition, such as restriction in the diet necessitated by lesions or dysfunction of the gastro-intestinal tract In discussing their cases, Eusterman and O'Leary reviewed the literature of the subject and concluded that this "secondary form of pellagra tends to support the theory that dietary deficiency is the cause of the disease" Crutchfield<sup>13</sup> also, in his analysis of 109 cases of pellagra in the John Sealy Hospital in Galveston, pointed to the number of instances in which the symptoms of the disease developed secondary to some disturbance of nutrition and cleared up when such interfering factors were removed

Records of the customary dietary practices of pellagrous patients or of families in which pellagra exists are less numerous Siler, Garrison and MacNeal<sup>2</sup> and Jobling and Peterson<sup>8</sup> considered the relation of diet to the incidence of pellagra as a part of their extensive surveys Both groups of investigators secured certain information regarding the food habits of all persons and families interviewed, such as the frequency with which certain foods were used and a typical day's menu In neither case were records secured of the foods actually purchased or consumed Boyd and McLean,<sup>7</sup> in their report of pellagra in Turkish prisoners of war, gave estimations of the value of the diets previous to capture, based on the statements of the prisoners and their officers These reports show general tendencies as to consumption of food, but do not furnish quantitative figures

Goldberger, Wheeler and Sydenstricker<sup>14</sup> were the first, so far as we are aware, to secure quantitative records of family food purchases over a period of time They secured records of the diets of non-pellagrous and pellagrous households in seven mill villages in South Carolina over a fifteen day period between April 15 and June 15 The records were classified according to family income and pellagrous state,

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11 Carley, P S Case of Pellagra Following Voluntary Restriction of Diet, *J A M A* **91** 879 (Sept 22) 1928

12 Eusterman, G B, and O'Leary, P A Pellagra Secondary to Benign and Carcinomatous Lesions and Dysfunction of the Gastro-Intestinal Tract Report of Thirteen Cases, *Arch Int Med* **47** 633 (April) 1931

13 Crutchfield, E D Pellagra with Special Reference to the Skin and Mucous Membrane, *Arch Dermat & Syph* **17** 650 (May) 1928

14 Goldberger, J, Wheeler, G A, and Sydenstricker, E H Study of Diet of Non-Pellagrous and Pellagrous Households, *J A M A* **71** 944 (Sept 21) 1918

and showed interesting differences in the consumption of milk, fresh meat and vegetables by the nonpellagrous and pellagrous families. Recently, the same group of investigators<sup>15</sup> has published records of food purchases in these same villages during different seasons of the year. The figures indicate considerable seasonal variation in the supply of fresh meat, milk and vegetables available, but are not analyzed to show the relative amounts of these used by pellagrous and nonpellagrous families.

Several writers have suggested that the causes of the disease are probably in operation months before the onset of the usually recognized symptoms. Boyd and McLean<sup>7</sup> postulated a "pre-pellagious" state on the basis of their studies of the coefficients of digestibility of protein in Turkish prisoners of war. They found a distinct decrease in the individual's ability to use the protein ingested weeks before the appearance of the symptoms on which diagnosis was based. Goldberger, Wheeler and Sydenstricker<sup>14</sup> suggested that the seasonal appearance of pellagra may be correlated with variations in the food supply, if it is assumed that the winter season with its restricted diet serves as a long period of depletion.

#### NEED FOR FURTHER DIETARY STUDIES

There appears to us to be a need for investigation of the diets of pellagrous persons at different seasons of the year and for comparison of these with diets collected under similar conditions from families free from the disease. Such studies should throw some light on the question of seasonal variation, and should bring into relief any important differences in the dietary practices of pellagrous and nonpellagrous persons.

The present study of family dietaries in Leon County, Fla., has been planned with these considerations in mind, in the hope of securing information concerning (a) seasonal variation in the diets of pellagrous families, and (b) any important differences in the choice of foods by this group as compared with nonpellagrous families.

#### METHODS USED IN PRESENT DIETARY STUDY

*Selection of Families*—The names of families in which one or more active cases of pellagra existed were secured through the courtesy of local physicians and welfare workers. Only those cases in which diagnosis had been made by a practicing physician were considered. Sixteen such families were found who were willing to cooperate in the study. In fifteen of these, the housewife was pellagrous, and where there were multiple cases of the disease in a family, the additional cases existed among the children. In only one family was the pellagrous member an adult man.

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<sup>15</sup> Goldberger, J., Wheeler, G. A., Sydenstricker, E. J., and King, W. I. A Study of Endemic Pellagra in Some Cotton Mill Villages of South Carolina, Hyg. Lab. Bull. 153, January, 1929.

For comparison with this group a control group was secured, consisting of thirteen families of similar occupational level who were free from the disease. Many of the families in this second group were friends or acquaintances of the pellagrous group.

The occupations of the principal wage earners in both groups were, in the order of their frequency, those of carpenter, painter, bus or truck driver, small store keeper, mechanic, farmer, fireman and nightwatchman. In two families of each group the principal wage earner reported doing only odd jobs.

Some of the families lived on the outskirts of Tallahassee, a city of about 10,000 inhabitants, while others lived in or near small settlements in the county. None were more than twelve miles from Tallahassee, and the majority came to town on Saturday for the weekly marketing.

*Selection of Seasons for Securing Dietary Records*—The seasons selected for collection of the family dietary records were midwinter (January and February), spring (June 1 to 15), late summer (August 25 to September 6) and fall (November 1 to 15), as it was believed that these periods would show the maximum effect of any seasonal influence which might exist. In this district there is seldom killing

TABLE 1—*Personal Data Concerning Families Studied*

Socio Economic Factors	Pellagrous Families	Nonpellagrous Families
Number of families reported	16	13
Average number in family	6.7	6
Average weekly money income	\$20.10	\$28.75
Main wage earner working full time	6	10
Main wage earner working part time	10	3
Families owning home	9	9
Average number of rooms in house	3.5	3.5
Houses with running water	4	5
Houses with sewerage	3	3

frost, and it is possible for the thrifty family to keep a supply of vegetables the year round. The average household, however, does not maintain a garden through the winter months. The great majority of families have a spring garden, which is at its best during May, June and the first part of July. The next two months usually show a decrease in garden produce because of the midsummer heat. The fall gardens are at their height from the middle of September until November or later.

*Methods of Securing Information*—The investigator visited the individual families, interviewing the housewife in each case. At the first visit certain personal data covering socio-economic factors were secured. Facts considered pertinent to this study are given in table 1. From this table it will be seen that the two groups were quite similar, though the weekly income of the control group was somewhat larger.

At this first visit an inventory was taken of all foods on hand and records were started jointly by the housewife and the visitor. Record sheets, one for each of the seven days of the experimental period, were left with the housewife to be used for recording purchases or foods otherwise secured on any of these days. Space was provided for giving the name, weight, price and place of purchase, or source, of each article. A second set of sheets was provided for recording the menus for each day. At the end of the seven day period, the investigator returned and checked the market lists and menu sheets to see that all essential information was listed, and to catch and correct any discrepancies between the two records. Foods left

on hand were noted and subtracted from the totals purchased. In general, the women were interested and cooperative, and kept records which were accurate to the best of their ability.

The inventories and market lists were relatively simple affairs, as most of the families marketed once a week and kept little reserve supply on hand.

Throughout the study, the investigator endeavored to maintain a neutral attitude and refrained from making any statements which might influence the family in its choice of food. The physicians diagnosing the cases undoubtedly exerted some influence, as the majority of them made recommendations for the improvement of the diet. This influence was not marked, however, as the limited incomes and meager knowledge of food values made it difficult for the women responsible for the purchase and preparation of the food to make radical changes in their dietary practices.

TABLE 2—*Number Seasons Represented by Family Diets*

Number of Seasons Represented	Total Families	Pellagrous Families	Nonpellagrous Families
4	14	7	7
3	9	6	3
2	4	1	3
1	2	2	0
Totals	29	16	13

TABLE 3—*Seasonal Distribution of Dietary Records*

Season	Records Collected at Seasons Specified		
	Total	Pellagrous Families	Nonpellagrous Families
January-February	27	15	12
June 1-15	26	14	12
August 27-September 6	21	12	9
November 1-15	19	9	10

At each season the method of securing the food records was the same, and any change in the make-up of the family was noted. Records were kept likewise of the variation in severity of symptoms of pellagra at the different seasons.

## RESULTS

A total of ninety-three family dietaries, each covering a period of seven consecutive days, were secured from twenty-nine individual families, sixteen of which had one or more members with active cases of pellagra, while the remaining thirteen families constituted the normal control group. Tables 2 and 3 give the number of seasons for which individual families kept records and the seasonal distribution of these.

The dietary returns have been analyzed in various ways in order that any significant differences in the diets from season to season or from group to group might be brought to light. Table 4 gives the total calories and grams of protein per adult male unit<sup>16</sup> per day for

<sup>16</sup> Atwater, W. O. Principles of Nutrition and Nutritive Value of Food, U. S. Dept. of Agriculture Farmer's Bull., 1918, no. 142, p. 30.

the pellagrous and the control families at each of the four seasons studied Table 5 shows the distribution of total calories among the food groups, (1) cereals, (2) milk, (3) vegetables and fruits, (4) sweets, (5) fats and (6) animal foods excluding milk The accom-

TABLE 4—*Total Calories and Protein Grams Estimated per Adult Male Unit per Day*

Season	Calories per Adult Male Unit per Day		Grams of Protein per Adult Male Unit per Day		Percentage of Total Calories from Protein	
	Pellagrous Families	Non pellagrous Families	Pellagrous Families	Non-pellagrous Families	Pellagrous Families	Non pellagrous Families
January February	3,544	3,985	84.3	100.8	8.8	10.0
June 1 15	4,176	4,001	94.5	96.2	8.9	9.5
August 27 September 6	3,899	3,351	105.2	96.1	10.8	11.1
November 1 15	3,649	4,616	98.0	121.2	10.2	10.4
Average for all seasons	3,817	3,963	95.5	104.3	9.7	10.2

TABLE 5—*Percentage Distribution of Total Calories Among Food Groups Specified at Different Seasons of the Year*

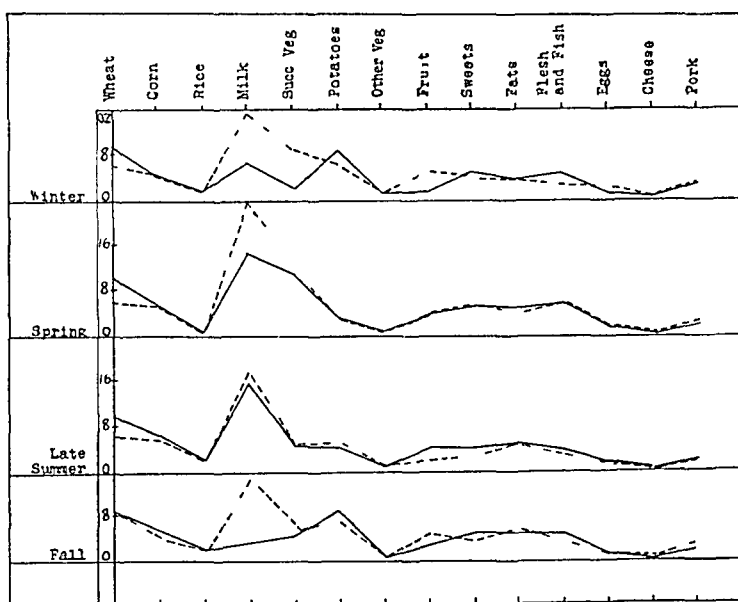
Food Group	Season	Pellagrous Group		Nonpellagrous Group	
		Range, per Cent	Mean, per Cent	Range, per Cent	Mean, per Cent
Cereals	January February	27.8-58.0	43.3	22.9-43.9	33.6
	June 1 15	31.4-54.7	42.0	26.4-48.1	38.1
	August 27 September 6	18.8-66.6	43.3	25.9-59.5	40.0
	November 1 15	25.0-71.9	40.9	16.7-56.6	33.3
Milk	January February	0.0-15.2	3.8	2.4-25.2	10.3
	June 1 15	0.0-15.6	5.8	3.1-29.2	11.3
	August 27 September 6	0.0-22.1	5.2	0.0-35.1	9.2
	November 1 15	0.0-4.0	2.6	1.0-12.0	6.3
Fruits and vegetables	January February	5.1-15.7	9.5	3.1-20.2	11.2
	June 1 15	2.5-12.9	7.1	2.6-9.5	6.3
	August 27 September 6	2.3-18.6	7.2	3.0-10.0	7.6
	November 1 15	1.5-20.2	11.0	9.0-18.0	12.6
Sweets	January February	6.5-18.4	12.3	1.7-16.5	11.3
	June 1 15	3.0-16.0	10.7	6.2-21.7	12.3
	August 27 September 6	1.6-21.7	10.2	0.0-17.8	5.8
	November 1 15	2.5-17.9	10.9	0.0-21.8	9.1
Fats	January February	7.0-32.4	19.6	8.8-31.7	20.6
	June 1 15	16.3-36.6	27.1	13.6-39.2	23.4
	August 27 September 6	4.8-44.6	23.2	0.0-43.4	23.9
	November 1 15	11.0-42.2	20.6	15.8-44.0	28.9
Animal foods except milk	January February	2.2-29.7	11.8	1.3-21.0	12.6
	June 1 15	0.0-13.2	6.7	2.0-22.9	8.9
	August 27 September 6	0.0-24.6	9.0	2.2-25.2	7.6
	November 1 15	2.6-22.5	11.8	0.0-19.2	9.8

panying chart presents graphically the distribution of the total food supply in ounces per adult male unit per day for the pellagrous and the nonpellagrous families at each season, and table 6 gives calculations of the differences in the use of certain foods by the two groups

It may be seen from table 4 that calories are liberal and total protein within normal limits for both groups Household waste probably accounts, in part, for the apparent high calorie value of the diets

The first important difference which appears is in the use of milk. In table 5 this difference is evident. When the amounts are expressed in ounces per adult male unit per day, as in table 6, the difference is marked, being almost three times the probable error in the winter diets and over five times the probable error in the fall diets.

A second difference of almost equal importance appears in table 6, in the use of succulent vegetables by the two groups. In the winter diets the difference in favor of the nonpellagrous families is more than three times the probable error, while in the fall records it is more than two. This difference is masked in table 5 by the inclusion of potatoes in the vegetable group.



Graph of the food supply of nonpellagrous and pellagrous families at different seasons of the year, estimated in ounces per adult male unit per day. Pellagrous families, —, nonpellagrous, ----

The use of cereals by the pellagrous families seems somewhat greater than that by the control families. The chart shows that wheat was used to a greater extent than corn, and that the latter was used in about the same amount by both groups. There is some indication of a difference in the amounts of eggs, cheese and fruit used, but the individual differences are too great for this to be more than suggestive. The amount of fats and sweets used is very similar in both groups. The same is true of the use of flesh and fish, a result somewhat different from that which the experience of earlier investigators<sup>14</sup> would lead one to expect.

Both table 6 and the chart show seasonal variation in the supply of milk and succulent vegetables, a variation that is greater in the pellagrous than in the nonpellagrous diets. It would seem that the food supply

TABLE 6—*Supply of Certain Foods per Adult Male Unit per Day for Different Seasons of the Year*

Ounces per Adult Male Unit per Day at Specified Seasons												
Winter				Early Summer				Late Summer				Fall
Pella group	Non pella group	Difference		Pella group	Non pella group	Difference		Pella group	Non pella group	Difference		Pella group
Group	Group			Group	Group			Group	Group			Group
												Group
												Difference
												Difference
Cereals	15 65	13 62	2 03 ± 1 10	17 54	14 03	3 46 ± 1 50	18 43	13 40	5 03 ± 1 44	16 14	14 53	1 61 ± 1 96
Milk	6 85	15 87	9 02 ± 3 32	14 83	23 03	8 20 ± 4 90	15 01	16 95	1 94 ± 3 35	3 34	14 66	11 32 ± 2 70
Succulent vegetables	2 05	8 80	6 75 ± 2 15	10 87	11 53	0 66 ± 1 51	4 30	5 88	1 58 ± 0 90	4 13	6 79	2 66 ± 1 14
Potatoes	9 22	6 26	3 96 ± 1 56	3 06	3 23	0 17 ± 0 23	4 00	4 69	0 69 ± 1 02	8 31	8 50	0 16 ± 1 01
Fruit	1 29	4 80	3 51 ± 1 18	3 82	3 26	0 56 ± 1 10	3 51	1 33	2 18 ± 1 30	2 30	4 05	1 75 ± 1 30
Eggs	0 95	1 71	0 76 ± 0 31	1 49	1 55	0 06 ± 0 49	0 85	0 92	0 07 ± 0 56	0 76	1 05	0 29 ± 0 50
Cheese	0 03	0 27	0 19 ± 0 11		0 45		0 09	0 11	0 02 ± 0 10	0 05	0 17	0 12 ± 0 10
Flesh and fish (except pork)	4 44	2 86	1 58 ± 0 71	5 23	5 61	0 38 ± 1 37	3 43	2 97	0 46 ± 0 83	4 66	3 63	1 03 ± 1 21
Pork, lean	2 42	2 38	0 04 ± 0 57	0 50	1 38	0 48 ± 0 43	1 31	0 27	1 01 ± 0 76	1 82	2 03	0 21 ± 0 71

of the pellagrous group is more influenced by fortuitous circumstances than is that of the nonpellagrous families. When the food supply is abundant, the pellagrous family has a more liberal diet, but when the season is less favorable, little effort seems to be made to keep the diet uniform.

Records of recurrences of pellagra in the families studied show that the eruption appeared most frequently in March and April, before the increased food supply of the spring was available.

#### COMMENT

Milk has long been recognized as valuable in the prevention and treatment of pellagra. Roussel,<sup>17</sup> as early as 1845, stated that the most effective treatment of pellagra was a milk diet. Goldberger, Waring and Willets,<sup>18</sup> in their studies of institutional diets, found that an inverse relation existed between the use of milk and the incidence of the disease. Goldberger and Tanner<sup>19</sup> presented definite evidence of the value of whole milk, butter milk and dry skim milk in prevention and treatment of the condition. Siler, Garrison and MacNeal<sup>2</sup> found "that the families in which milk was not used were the ones in which pellagra appeared the most frequently, while on the other hand, those families using this food daily developed new cases the most infrequently." Wheeler<sup>20</sup> cited three cases to show that "in cases of borderline nutrition, where a slight unfavorable change in diet may put the family into the malnourished class, the milk supply may be the controlling factor in the appearance or non-appearance of the disease."

The present study confirms the earlier observations of an inverse relationship between the use of milk and the incidence of pellagra, and extends these findings in showing the existence of a seasonal variation in the milk supply of the families studied, which is sufficiently greater in the pellagrous diets to constitute a significant difference between the dietary practices of the two groups.

The seasonal variation in the use of succulent vegetables found in this study confirms the general observations to this effect, and here again extends earlier observations in showing that the variation is greater in the pellagrous families. We do not have as yet sufficient knowledge of the relative merits of individual vegetables to be able to discuss the importance of this variation in terms either of pellagra

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17 Roussel, cited in McCollum, E. V., and Simmonds, N. *Newer Knowledge of Nutrition*, ed. 3, New York, The Macmillan Company, 1925, p. 321.

18 Goldberger, Waring, and Willets (footnote 4, first reference).

19 Goldberger and Tanner (footnote 9, first reference).

20 Wheeler, G. A. *Pellagra in Relation to Milk Supply in Households*, U. S. Pub. Health Rep. **39** 2197 (Aug. 29) 1924.



preventive, blacktongue preventive or vitamin G values. There is no doubt, however, that the general nutritional value of the monotonous and limited dietaries would be improved by the liberal and uniform use of these foods.

A study of twenty-nine families is too limited in scope to warrant generalizations. The results, however, would seem to justify emphasis, in practical dietary recommendations, on the need for an increased use of succulent vegetables during the months when garden produce is less plentiful and for the establishment of a uniformly liberal milk supply throughout the year.

#### SUMMARY AND CONCLUSIONS

1 A study has been made of the dietaries of twenty-nine families in Leon County, Fla. Active cases of pellagra existed in sixteen of these, while the members of the remaining thirteen families were free from the disease. Dietary records to the number of ninety-three, each covering a period of seven days, have been collected at different seasons of the year, namely, midwinter, spring, late summer and fall.

2 Comparison of the records of the pellagrous and the control groups shows significant differences in the use of milk and succulent vegetables, particularly in the fall and winter diets, with some indications of a difference in the use of eggs, cheese and fruit. The use of lean meat and fish is similar in both groups.

3 Evidence of a distinct seasonal variation in the supply of milk and succulent vegetables is presented, which confirms the observations of previous investigators and extends their findings in showing that this seasonal influence is sufficiently more marked in the dietaries of the pellagrous families to constitute an important difference in the dietary practices of the two groups.

# UNDULANT FEVER

AN EPIDEMIC OF SUBCLINICAL INFECTION WITH BRUCELLA

PARKER DOOLEY, M D

KENT, CONN

In recent years, so much has been written about infection with *Brucella* that it seems advisable to limit this report to the briefest and most objective description of my own experience. For excellent reviews, with bibliographies, the reader is referred to the publications of Hardy<sup>1</sup> and of Löffler,<sup>2</sup> and to the report of the League of Nations<sup>3</sup>

The persons dealt with in this study were the pupils, masters and employees in a boys' boarding school in a rural region of Connecticut, where I have been in continuous resident attendance for the past three years. Excellent hospital equipment, with adequate nursing care, and laboratory facilities, with technical assistance, are an integral part of the school. Individual medical records with notation of every complaint, however trivial, are carefully kept. During the winter term, each boy is briefly examined every day, and during the rest of the school year frequent examinations are made. This close personal supervision, together with the laboratory facilities available, creates an opportunity for clinical observation that is almost unique.

For many years, the entire milk supply of the school has come from the school dairy, containing about a hundred Holstein cows. In 1925, there was an epidemic of contagious abortion in this herd, about a dozen cows losing their calves prematurely. Apparently, there was no reflection of this bovine epidemic in the general health of the members of the school community at that time. As there had been no sign of infection in the herd in five years, it was assumed that the herd was free from the disease, and the milk was rated as certified, grade A milk.

Because raw milk was being used in the school, a serum agglutination test for *Brucella* was tried on nearly every boy who entered the infirmary with fever, no matter what the apparent cause. Furthermore, a number of agglutination tests were made on boys who had not been sick, as I was interested in finding the incidence of agglutinins in normal per-

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1 Hardy, A. V. Undulant Fever, Washington, D. C., National Institute of Health Bull. 158, Dec., 1930.

2 Löffler, W. Febris undulans Bang des Menschen, Wurzburger Abhandlungen der Gesamtgesellschaft der Med. 26: 365, 1930.

3 Epidemiol. Rep., League of Nations 9: 409 (Oct. 15) 1930.

sons who had been drinking large quantities of raw milk. As all of these tests were negative prior to Nov 27, 1930, it is known definitely that agglutinins developed in a considerable number of boys within a certain period. Suddenly, on November 27, a boy fell sick with a severe febrile illness which was diagnosed as undulant fever, this case has been reported elsewhere<sup>4</sup>. As soon as this diagnosis was established, the herd was reinvestigated. It was found that one cow had dropped a pair of weak twin calves a few days before time, on November 13. Her milk was first used on November 18. This cow and four others of the herd were found to give positive reactions when their serums were tested for agglutinins with an antigen made from four strains of *Brucella* of bovine origin. Only three of the five cows were fresh at the time. These three had *Brucella* agglutinins in their whey also, but only the one that had calved prematurely was shedding *Brucella* organisms in her milk, so far as one could tell by inoculations of guinea-pigs. These cows were removed from the herd. Pasteurization of the milk at 63 degrees C for thirty minutes was started as soon as possible. No raw milk was used after December 20.

Many serum agglutination tests for *Brucella* had been done in the preceding year, but with the finding of a case of undulant fever in the student body, an intensive serum study was begun. From Dec 1, 1930, to Dec 1, 1931, 232 boys between the ages of 13 and 19 and 31 young adults were studied for the presence of serum agglutinins. All of these persons had been drinking large quantities of the infected milk for at least three months, and some had been drinking it for several years. With the exceptions to be noted, none of these persons had had any contact with animals. At least three separate routine agglutination tests were made on each person, while dozens of tests were made on some<sup>5</sup>. Blood cultures were made on each person studied,

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4 Dooley, P. Undulant Fever, *New England J Med* **204** 759 (April 9) 1931

5 In the school laboratory the technic for the agglutination test was essentially the same throughout this work. The organisms were grown for forty-eight hours on beef liver infusion agar, then washed off with physiologic solution of sodium chloride to which 0.1 per cent formaldehyde had been added. This antigen was diluted to 1:1,000 (silica standard, given in *Standard Methods of Water Analysis*, ed 6, New York, American Public Health Association, 1925, p 4). Unheated serum was used in dilutions of from 1:10 to 1:320, higher dilutions being used on positive serums. The final readings were made after twenty-four hours, eight in the incubator at 37 C and sixteen in the icebox between 5 and 15 C. The titers recorded indicate the maximum dilution in which there was complete clearing of the supernatant fluid. It was found that the titer curve for any given specimen varied with the dilution of the antigen, but did not vary appreciably with antigens made from the various strains isolated in the course of this study.

Several examinations of the stools and duplicate serum agglutination tests on more than 100 subjects were made in the laboratories of the Connecticut State

and were repeated if agglutinins were found in the serum. Unless there were clinical suggestions of disease, cultures of the stools and urine were made only on persons whose serums agglutinated above 1:160. Daily records of temperature were kept for all persons who showed agglutinins. Monthly weight charts were kept for all persons in the group. When a boy thus observed showed neither loss of weight nor failure to gain in weight and had no fever and no history of lassitude, weakness, malaise, sweating, chilliness, loss of appetite, nervousness, cough, headache, backache, abdominal pain or constipation, it seemed safe to say that he had not had undulant fever, no matter how high his agglutinin titer against *Brucella* organisms may have been. Furthermore, when fever and signs of infection of the upper respiratory tract developed in a boy, at a time when other boys, without such agglutinins,

TABLE 1—*Results of Agglutination Tests*

Greatest Dilution of Complete Agglutination During Study	Number of Persons Tested	Percentage of Persons Tested	Number of Persons Who Had Any Form of Febrile Illness	Percentage Who Had Such Illness
Negative	155	58.7	57	37
1:10 to 1:40	62	41.3	17	34
1:80 to 1:160	32		13	
1:320 to 1:640	6		3	
1:1,280 to 1:2,560	5		1	
1:5,120 to 1:12,000	4		3	

showed the same signs and reacted in the same way, it seemed unreasonable to relate his illness to *Brucella* infection, no matter how high his agglutination titer may have been.

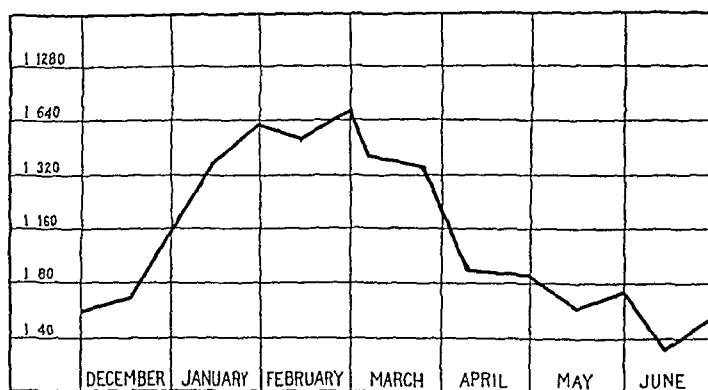
The results of the study of agglutination are shown in table 1, in which it will be seen that 41.3 per cent of the persons studied showed agglutinins against *Brucella* in some dilution. The fact that a group of young children who used this same milk showed no serum agglutination has been discussed elsewhere.<sup>6</sup> Table 1 presents a statistical artefact, as the tests were not done on all of the group simultaneously but at various times over six months. Doubtless, a number of persons who showed relatively low titers would have had higher ones had they been tested earlier. Enough persons were tested frequently over

Department of Health by permission of Mr F. L. Mickle. Dr Elizabeth Parsons, director of laboratories of the West Virginia State Department of Health, identified some of the strains of *Brucella* isolated from patients and carried out numerous duplicate agglutination tests. *Brucella* strains isolated in the school laboratory were identified serologically, by agglutinin absorption, as *Abortus*, with the help of Dr R. E. Dyer of the National Institute of Health.

<sup>6</sup> Dooley, P. Incidence of Undulant Fever in Children, *Arch. Dis. Childhood* 6:235 (Aug.) 1931.

this period to make it certain that the height of the epidemic, so far as agglutinin titers are concerned, was in January and February, and that there was a general decline in the ensuing three months (chart 1) In any case, the possibility of error lies in placing persons in a low titer group who may well have had much higher titers earlier

Two persons had definite undulant fever, as evidenced by the clinical course, the finding of *Brucella* organisms in the blood and stools and the presence of serum agglutinins Their serum titer curves over one year are shown in table 2, in which they are listed as cases 1 and 2 Five other persons (cases 3 to 7, table 2) had infections of the upper respiratory tract with fever at some time during the year, these febrile infections in association with high serum titers suggesting undulant fever even though the other laboratory findings and the clinical courses



The average titer of agglutination tests by two week periods In a crude way, this indicates the course of the infection in terms of agglutinin formation

did not suggest that diagnosis If one may assume that the time of exposure began with the use of the milk from the one cow, the first case occurred on the tenth day after the first exposure and the second case on the thirtieth day after the first exposure and the seventh day after the last exposure The incubation period for this disease has been variously estimated at from three days to three weeks Apparently it was ten days in the first case and an indeterminate time in the second The doubt as to whether the condition in the other cases is to be considered as undulant fever is so great as to permit no conclusions about the incubation period The patients in cases 8 to 15 (table 2) had no illness and did not show *Brucella* organisms in the blood, stools or urine at any time, despite the fact that repeatedly verified serum agglutination tests were positive in high dilutions (1:5,120 in 2 cases) These findings are presented because they seem to indicate that persons can be infected with *Brucella* and yet give no clinical evidence of such

TABLE 2—*Serum Agglutination of Persons Whose Serum Gave a Positive Reaction in the Dilution of 1 320 at Any Time During the Study*

Case	1930				1931										
	March	May	October	December	January	February	March	April	May	June	September	October	November	December	
1			Negative	1 2,560	1 12,000	1 5,120	1 1 280			1 160	Negative			Negative	
2					1 2,560	1 5,120		1 320		1 80					
3					1 1,280	1 2,560			1 640		1 80			1 20	
4							1 640			1 640		1 80		1 80	
5					1 160	1 640				1 80			Negative		
6						1 320			1 120					Negative	
7						1 5,120	1 5,120	1 2,560	1 1,280	1 640					
8			Negative		1 2,560	1 5,120	1 2,560	1 640	1 320	1 320	1 120	1 120		1 120	
9							1 2,560			1 1,280		1 120			
10									1 320	1 320			1 120		
11								1 1,280				1 120			
12								1 1,280		1 320				Negative	
13				1 40				1 640		1 120					
14							1 320			1 20	Negative			Negative	
15					1 1,280			1 640		1 320		1 20		1 20	

infection King and Caldwell,<sup>7</sup> Hardy,<sup>1</sup> Hasseltine,<sup>8</sup> Huddleson and Johnson<sup>9</sup> and Jordan<sup>10</sup> have recorded studies in which this seemed true

In an isolated and closely associated group of persons such as this one, minor epidemics of infection of the upper respiratory tract with fever recur throughout the year. One wonders whether persons with agglutinins against *Brucella* are more susceptible to such infection than those without agglutinins. In table 1, it appears that 34 per cent of those with agglutinins had some form of febrile illness, while 37 per cent of those without agglutinins had such illness. Comparison of the individual records of those with infection of the upper respiratory tract shows that the average duration of illness was approximately the same in the two groups. The figures for the incidence of respiratory infection include the entire year and not just the period of the study of agglutination recorded in the rest of the table.

In 11 boys who on several occasions had been found to have positive agglutination tests against *Brucella* in low dilutions (1:10 to 1:40) febrile illnesses developed which could not be confused with undulant fever, however atypical. These illnesses included pertussis, varicella, follicular tonsillitis due to beta-hemolytic streptococci, serum sickness and reaction to typhoid vaccine. Seven of these boys showed a quick increase in serum agglutinins, in one instance an increase from 1:80 to 1:640 in one week. Apparently fever due to any cause may increase serum agglutinins against *Brucella*, whether the person has or has not had a clinical infection with undulant fever in the past. These findings make one particularly cautious in accepting the diagnosis of undulant fever whenever a fever of unknown etiology is associated with a positive agglutination test, even when the titer is high. Apropos of this, Gilbert and Coleman,<sup>11</sup> working with typhoid fever, concluded that "fluctuation of the agglutinin titer, considered by some as definite evidence of typhoid infection, may occur in cases in which this infection is definitely excluded."

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7 King, M. J., and Caldwell, D. W. Undulant Fever, *Am J M Sc* **178** 115, 1929

8 Hasseltine, H. E. Study of the Epidemiology of Undulant Fever, *Am J Pub Health* **21** 519 (May) 1931

9 Huddleson, I. F., and Johnson, H. W. Brucellosis, *J A M A* **94** 1905 (June 14) 1930

10 Jordan, C. F. Infection in the Epidemiology of Undulant Fever in the General Population and in Selected Groups in Iowa, *J Infect Dis* **48** 526 (June) 1931

11 Gilbert, R., and Coleman, M. B. Agglutination of Typhoid Bacilli of Patients Having Unrelated Infections, *J Infect Dis* **46** 311 (April) 1930

As many cases of undulant fever have been reported as the result of laboratory infection, it is worth noting that neither of the technicians, who handled cultures and live antigens almost daily for more than a year, showed agglutinins in their serums. One of them had used none of the raw milk, the other, very little of it. Of the entire group, the four dairymen, all of whom had negative serum, are the only ones who ever came in contact with animals.

Perhaps the most significant feature of this study has been the finding of agglutinins in persons who could not have had undulant fever. Under certain conditions, perhaps whenever small quantities of *Brucella* organisms of relatively low virulence are ingested over long periods, antibodies develop in the absence of undulant fever. The protean character of the clinical manifestations of undulant fever is so generally appreciated that there may be a tendency to call any illness undulant fever when there are agglutinins in the patient's serum. It appears that one must be cautious in making this diagnosis in clinically atypical cases unless the organism can be recovered.

#### SUMMARY

Forty-one per cent of 263 persons using infected raw milk were found to have serum agglutinins against *Brucella abortus*.

Of those whose serums agglutinated in the dilution of 1:320 or above two had clinical undulant fever, five had febrile illnesses other than undulant fever and eight had no illness.



# LOW VOLTAGE IN THE ELECTROCARDIOGRAM

## OCCURRENCE AND CLINICAL SIGNIFICANCE

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In the course of the routine interpretation of electrocardiograms, records are frequently encountered in which the Q-R-S complexes are small. The condition is called "low voltage" when the greatest excursion is less than 5 mm in amplitude in all three leads<sup>1</sup>. It is not uncommon. At the Presbyterian Hospital it was found thirty-one times in the last thousand records, an incidence of 3 per cent. Despite the frequency of this electrocardiographic abnormality, a review of the available literature leaves its significance uncertain. Because of the doubt covering its interpretation, the cases of low voltage at this hospital have been reviewed with the hope of gaining further insight into the occurrence and clinical significance of this deviation from the normal electrocardiogram.

### REVIEW OF THE LITERATURE

Waves of low amplitude were first noted as a part of the electrocardiographic picture in the disturbance of intraventricular conduction formerly called "arborization block"<sup>2</sup>. Low voltage was also described in hypothyroidism, in which condition it tended to disappear as the basal metabolism returned toward normal with appropriate therapy<sup>3</sup>. The

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From the Department of Medicine, College of Physicians and Surgeons of Columbia University, and the Presbyterian Hospital.

1 Criteria for the Interpretation of Electrocardiograms, New York, New York Tuberculosis and Health Association, 1931. Some authors have adopted less rigid standards and have said that low voltage was present when the complexes were less than 5 mm in amplitude in one or two leads only, or even when the greatest excursion was less than 1 cm. In the present paper the arbitrary but more commonly accepted criterion has been adhered to, as stated.

2 Carter, E. P. Further Observations on the Aberrant Electrocardiogram Associated with Sclerosis of the Atrioventricular Bundle Branches and Their Terminal Arborizations. Clinical and Histologic Report of a Case in Which Such Aberrant Complexes were Obtained, *Arch Int Med* **22** 331 (Sept) 1918. Oppenheimer, B. S., and Rothschild, M. A. Electrocardiographic Changes Associated with Myocardial Involvement. With Special Reference to Prognosis, *J A M A* **69** 429 (Aug 11) 1917, The Value of the Electrocardiogram in the Diagnosis and Prognosis of Myocardial Disease, *Tr A Am Physicians* **39** 247, 1924.

3 Zondek, H. Das Myxodemherz, *Munchen med Wchnschr* **65** 1180, 1918. Thacher, C., and White, P. D. The Electrocardiogram in Myxedema, *Am J M Sc* **171** 61, 1926. Reid, W. D., and Kenway, F. L. Electrocardiographic Signs Associated with Low Basal Metabolism, *Endocrinology* **13** 191, 1929.

work of a number of German investigators has shown that in these cases the electrocardiographic finding is the result of an increased electrical capacity of the skin and is not due to a fundamental change within the muscle of the heart <sup>4</sup>

A decrease in the venous flow to the heart or a change in cardiac position has been noted to cause a lowering of the voltage <sup>5</sup> In both clinical and experimental pericardial effusion low voltage may be present <sup>6</sup> Low voltage has been associated by some authors with definite cardiac disease <sup>7</sup> Sprague and White, in 1926, reported a series of fifty-seven cases from the Massachusetts General Hospital <sup>8</sup> From their study of this series the authors concluded that low voltage was of serious prognostic import, and that it did not occur in electrocardiograms of normal hearts Hepburn and Jamieson,<sup>9</sup> in the same year, reached similar conclusions The series reported by these authors differed from that of Sprague and White in that all cases showing evidence of myocardial damage or such abnormalities of mechanism as auricular fibrillation were excluded In the following year, Willius, from a review of the material at the Mayo Clinic, reached the conclusion that low voltage, in the absence of other abnormalities in the electrocardiogram, was of no significance <sup>10</sup> These two conflicting views dominate the literature

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4 Lueg, W Haut und Elektrokardiogramm, Arch f d ges Physiol **212** 649, 1925, Ueber das Elektrokardiogramm des Myxodems, Ztschr f klin Med **104** 337, 1926, Ueber das Elektrokardiogramm des Myxodemherzens, Deutsche med Wchnschr **53** 319, 1927, Elektrochemische Untersuchungen der menschlichen Haut, Ztschr f klin Med **106** 21, 1927 Nobel, E, Rosenbluth, A, and Samet, B Das Elektrokardiogramm des kindlichen Myxodems, Ztschr f d ges exper Med **43** 332, 1924

5 Otto, H L Effect of Altering Venous Inflow to the Heart on the Voltage of the Electrocardiogram, Proc Soc Exper Biol & Med **26** 202, 1928, Effect of Altering Position of the Heart on the Voltage of the Electrocardiogram, *ibid* **26** 204, 1928

6 Katz, L N, Feil, H S, and Scott, R W The Electrocardiogram in Pericardial Effusion II Experimental, Am Heart J **5** 77, 1929 Oppenheimer, B S, and Mann, H An Electrocardiographic Sign in Pericardial Effusion, Proc Soc Exper Biol & Med **20** 431, 1923

7 White, P D, and Burwell, C S The Clinical Significance of Changes in the Form of the Electrocardiogram, M Clin North America **4** 1839, 1921 Pardee, H E B, and Master, A M Electrocardiograms and Heart Muscle Disease, J A M A **80** 98 (Jan 13) 1923 Master, A W, and Pardee, H E B The Effect of Heart Muscle Disease on the Electrocardiogram, Arch Int Med **37** 42 (Jan) 1926 Burnett, C T, and Piltz, G F Low Voltage in the Electrocardiogram, Am Heart J **2** 649, 1927

8 Sprague, H B, and White, P D The Significance of Electrocardiograms of Low Voltage, J Clin Investigation **3** 109, 1926

9 Hepburn, J, and Jamieson, R A The Prognostic Significance of Several Common Electrocardiographic Abnormalities, Am Heart J **1** 623, 1926

10 Willius, F A, and Killins, W A The Occurrence and Significance of Electrocardiograms of Low Voltage, Arch Int Med **40** 332 (Sept) 1927

As a possible explanation of the mechanism of low voltage, Wilson<sup>11</sup> has recently pointed out "that any increase in the conductivity of the body tissues, particularly of those tissues which lie in close proximity to the heart, will decrease the amplitude of the electrocardiographic deflections

The question arises, therefore, as to whether edema of the lungs, pericardial effusion, hydrothorax, ascites or massive edema of all the body tissues may not decrease the amplitude of the electrocardiographic deflections." In such an event it would seem that the prognosis of a given case should be independent of the electrocardiographic finding and dependent entirely on such factors as the degree of cardiac insufficiency and the type of heart disease. Other authors have suggested or hinted that the cause of low voltage might be present within the muscle of the heart itself, i. e., that a poorly functioning myocardium might be incapable of producing enough difference in electrical potential at the surface of the body to produce waves in the electrocardiogram of normal amplitude.

#### MATERIAL

Low voltage was present in the electrocardiograms of 194 patients who entered the Presbyterian Hospital between 1921 and 1930. For the purposes of this study the histories of these cases have been analyzed. The electrocardiographic records in which low voltage occurred were examined, and the standardization of each lead was determined to be correct, i. e., the introduction of 1 millivolt of current produced a deflection of the string of 1 cm. Low voltage was said to be present when the greatest deflection of a properly standardized string was less than 5 mm in all of the three standard leads. All cases of low voltage were included regardless of whether there were or were not other coincident electrocardiographic abnormalities. That such a step was justifiable may be seen from the details of the analysis to be presented. It was found necessary to exclude 30 cases from the group because of inadequate clinical data. This left a series of 164 cases for analysis.

The 164 cases fell readily into 2 large groups. In the first were 113 patients with various forms of heart disease. In the second group were 51 patients with a multiplicity of diseases, which will be considered in detail.

#### OCCURRENCE OF LOW VOLTAGE IN PATIENTS WITH HEART DISEASE

The 113 patients in this series were subdivided into the following groups:

*Group I Patients with Heart Disease with Congestive Failure* — Sixty-three of the 113 patients with heart disease presented symptoms

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<sup>11</sup> Wilson, F. N. The Distribution of the Potential Difference Produced by the Heart Beat Within the Body and at Its Surface, *Am Heart J* 5:599, 1930.

and signs of slight to severe cardiac insufficiency, including the presence of abnormal distribution of fluid, varying from slight edema to general anasarca. There were 38 male and 25 female patients. The age range was from 13 to 80 years, with an average age of 53. On the basis of etiology, the cases were divided as follows: arteriosclerotic heart disease (including hypertension), 40, rheumatic, 17, syphilitic, 5, unclassified, 1.

In these cases low voltage appeared to be closely associated with congestive failure, was present only when combined with congestive failure, but was not invariably present when congestive failure appeared. In the electrocardiograms of fifty-four patients there was evidence of myocardial damage or of a disorder of the cardiac mechanism in addition to the low voltage. In only nine cases was low voltage the only abnormal finding.

Only a single electrocardiogram was taken in each of sixteen cases. In the remaining forty-seven cases there were two or more records. In thirty-three of the forty-seven cases the low voltage was a transient phenomenon, almost invariably occurring in the first records taken after admission and disappearing with the restoration of compensation. In six cases this sequence was reversed, and the low voltage, while absent in the initial electrocardiograms, appeared as a terminal finding at a variable period before death. In eight patients who were more or less decompensated throughout their period of observation, low voltage was a constant finding.

The following cases are typical examples of this group.

CASE 1—G. K., a white woman, aged 45, entered the hospital on Oct. 2, 1929, because of cardiac decompensation. The diagnosis was arteriosclerotic heart disease with hypertension, cardiac hypertrophy and auricular fibrillation. In an electrocardiogram taken on the day of admission the voltage was low. Additional findings were auricular fibrillation, inversion of  $T_1$  and left axis deviation. The patient was digitalized and responded with a most satisfactory and rapid clinical improvement accompanied by a marked diuresis. A second electrocardiogram taken two days after admission showed that the low voltage had disappeared, in a third record taken five days later it had not recurred.

This is an example of low voltage present as a transient finding in a patient decompensated on admission to the hospital and disappearing with restoration of compensation. In the next case, low voltage occurred as a terminal event.

CASE 2—A. J., a white man, aged 59, was admitted to the hospital on Feb. 20, 1925, with a diagnosis of arteriosclerotic heart disease, cardiac hypertrophy, auricular fibrillation and moderate cardiac insufficiency. An electrocardiogram taken on admission showed waves of normal amplitude, auricular fibrillation and a disturbance in the intraventricular conduction. Despite rest and the administration of digitalis, the course was rapidly downhill, with increasing decompensation. Ten

days after admission a second electrocardiogram again showed normal voltage. Three weeks later low voltage had appeared. By this time the patient was irrational and was transferred to another hospital, where, shortly afterward, he died.

In the following case low voltage was "permanent" in the sense that it was present on admission and persisted to the death of the patient.

CASE 3—J. B., a white man, aged 53, suffering from arteriosclerotic heart disease, was admitted to the hospital because of marked cardiac decompensation. The electrocardiogram taken on admission showed a few ventricular extrasystoles and low voltage. On the tenth day low voltage was again present, as was the case on the seventeenth day. There was no improvement in the patient's condition, and he died on the twenty-third day in the hospital.

*Group II Patients with Heart Disease Without Congestive Failure*  
—In this group there were forty-three patients. In none of these cases was there clinical evidence of congestive failure nor did x-ray pictures, which were taken in many instances, reveal evidence of pleural or pericardial effusions. All the patients had definite organic heart disease. Pain was the presenting symptom in many. There were twenty-nine male and fourteen female patients in this group. The age range was from 18 days to 79 years, with an average age of 54 years.

Classified according to etiology, thirty-three cases belonged to the group with arteriosclerotic heart disease, eight patients had rheumatic heart disease, and there was one case each of syphilitic and of congenital heart disease. Evidence of associated myocardial damage or a disorder of the cardiac mechanism such as auricular fibrillation was present in addition to low voltage in the electrocardiograms of thirty patients. In thirteen cases low voltage was the only finding of importance. This latter figure is notably higher than that for the group with congestive failure.

As to the duration of low voltage, it is unfortunate that in twenty of the forty-three cases in this group only one record was taken. In seventeen instances low voltage was a transient phenomenon, differing, however, from its occurrence in the group with congestive failure in that it was not so strikingly confined to the initial record or to the first few records after admission. In fact the contrary was apt to be the case, and low voltage usually occurred sporadically through a series of electrocardiograms on a given patient. For instance, in one patient the first three records during an admission to the hospital showed waves of normal amplitude, the next two showed definite low voltage, and the next two were again normal. Or, again, this sequence was seen: normal voltage in the first record, low voltage in the second and a return to normal in the next two.

In only one case did low voltage appear for the first time as a part of the terminal events. Where two or more records were taken low voltage was constantly present in five patients.

An example of the occurrence of low voltage in this group is presented in the following case

CASE 4—G S, a white woman, aged 70, was admitted to the hospital a few days after a coronary occlusion. Physical examination revealed no evidence of decompensation. The patient's chief complaint was cardiac pain that had been persistent from the onset of the occlusion, but was diminishing in severity. An electrocardiogram taken two days after admission showed only low voltage. Three days later the pain had disappeared entirely, the patient was comfortable, and the electrocardiogram was normal. A third record taken eleven days later, on her sixteenth day in the hospital, was again normal. On the seventeenth day, a second coronary thrombosis occurred. An electrocardiogram taken on the twenty-first day showed a recurrence of low voltage. No subsequent records were secured.

*Group III Patients with Heart Disease not Included in the Preceding Groups*—Seven cases could not be classified satisfactorily in the foregoing groups according to the presence or absence of congestive failure. Because of the unusual interest of this small group of patients with regard to the occurrence of low voltage, the seven case histories have been summarized.

CASE 5—F M, a white woman, aged 44, was admitted to the hospital on Sept 14, 1930, because of severe cardiac insufficiency due to rheumatic heart disease with stenosis and insufficiency of both the mitral and the aortic valves. An electrocardiogram taken on September 15 showed sinus rhythm, incomplete bundle branch block and many auricular premature beats. The waves were of normal amplitude. On September 19, a similar record was obtained. By September 25, the sinus rhythm had been replaced by auricular fibrillation. The voltage remained normal. A fourth record taken on September 29 was similar to the third. The patient's course during this period was one of steady clinical improvement. An electrocardiogram taken on October 6 showed that the auricular fibrillation and the incomplete bundle branch block were still present, but, in addition, low voltage was now present for the first time. Another record showed no change on October 14. At this time the patient had reached the peak of her improvement. Sinus rhythm reappeared in the electrocardiogram of October 20, although the block and low voltage persisted. About October 23 it was noted that the patient's condition was worse, and from that date her course was steadily downhill until she died, on November 15. Further electrocardiograms were taken on October 27 and on November 3. They were practically identical with the record of October 23. The low voltage persisted.

*Comment* The preceding case is interesting because the low voltage, which was absent on admission during a serious cardiac break, appeared at the height of clinical improvement and antedated by over two weeks a turn for the worse in the patient's clinical condition which led to a fatal outcome.

CASE 6—L S, a woman, aged 21, who had rheumatic heart disease, was admitted to the hospital markedly decompensated. On the next day, an electrocardiogram showed a rate of 120 beats per minute, auricular extrasystoles and a

shifting pacemaker The voltage was normal On her second day in the hospital, the heart rate became very rapid An electrocardiogram disclosed that this was an auricular tachycardia The rate was 200, and low voltage had appeared A few hours after the record was taken the patient died

Comment In this case low voltage was not present when the patient was admitted with severe congestive failure, but developed a few hours before death, coincidently with the appearance of an ectopic auricular tachycardia

CASE 7—N S, an Irish woman, aged 54, with diabetes mellitus and marked general arteriosclerosis, entered the hospital following a coronary thrombosis Electrocardiograms taken on the second, sixteenth, twenty-seventh and thirty-third days in the hospital showed successive changes in the T waves thought to be characteristic of the sequence seen after a coronary occlusion Low voltage was observed in each of these records, although cardiac insufficiency was not present On her forty-first day in the hospital, a fifth electrocardiogram showed that the low voltage had disappeared The patient was discharged four days later apparently in good condition A few weeks later pneumonia developed and she was readmitted At this time, she showed moderate cardiac insufficiency with edema of the ankles Low voltage reappeared in the electrocardiogram Only one record was secured during this admission

Comment In this patient low voltage appeared following a coronary accident but without demonstrable cardiac insufficiency It disappeared coincidently with improvement in the patient's condition, and reappeared later when she developed cardiac insufficiency precipitated by pneumonia

CASE 8—I A, a white man, aged 51, with arteriosclerotic heart disease, was admitted to the hospital severely decompensated on June 7, 1929, he was discharged on September 16 While in the hospital he showed slow but steady improvement, and on discharge his heart was considered well compensated During this period, eleven electrocardiograms were taken All records showed left axis deviation, inversion of T<sub>1</sub> and low voltage In the follow-up clinic, where he was observed for three months after discharge, a similar record was obtained

Comment Low voltage was present in this case on admission, when the patient was severely decompensated Although compensation was restored, the low voltage persisted and was again present in the follow-up clinic

CASE 9—S S, a white woman, aged 42, was admitted to the hospital severely decompensated She was found to have rheumatic heart disease with mitral stenosis and insufficiency and auricular fibrillation Electrocardiograms taken on her first, second and third days in the hospital showed auricular fibrillation and right axis deviation Low voltage was not present The patient improved satisfactorily until the beginning of her second week in the hospital when pneumonia developed, she died six days later During the course of the pneumonia, cardiac insufficiency again became manifest, and on the tenth day in the hospital a final electrocardiogram showed that low voltage had appeared

**Comment** Low voltage, which was absent during the congestive failure that was present on admission, appeared during a return of cardiac insufficiency due to a terminal pneumonia

**CASE 10**—J J, a white man, aged 57, was admitted to the hospital the first time following thrombosis of a coronary artery. There was no evidence of cardiac insufficiency. In fact, at first the patient afforded a diagnostic problem, as all his pain was abdominal. An electrocardiogram showed an iso-electric  $T_1$  and low voltage. Seven months later he was readmitted because of cardiac insufficiency. Two electrocardiograms taken during this admission each showed low voltage. A month later the patient was admitted for a third time because of recurrence of edema and dyspnea. Again an electrocardiogram showed low voltage.

**Comment** In this case low voltage was present on the first admission in the absence of cardiac insufficiency. On two subsequent admissions with cardiac failure low voltage persisted.

**CASE 11**—J L, a man, aged 36, gave a history on admission to the hospital extremely suggestive of coronary thrombosis, despite his relatively youthful age. The pain and shock had been followed rapidly by cardiac insufficiency, with the result that at the time of admission he was severely decompensated. An electrocardiogram taken shortly after entry showed marked deformity of the Q-R-S group but the waves were of normal amplitude. On his twelfth day in the hospital, he had a pulmonary embolus. On that day an electrocardiogram showed low voltage. Five days later the voltage was again normal and remained so until discharge after nearly three months.

**Comment** Low voltage, which was absent when the patient was admitted with marked cardiac insufficiency, appeared temporarily following pulmonary infarction.

#### OCURRENCE OF LOW VOLTAGE IN PATIENTS WITHOUT OBVIOUS HEART DISEASE

There were fifty-one patients whose electrocardiograms showed low voltage but who clinically did not present evidence of cardiac disturbance. It is not surprising that this series is smaller than the group with manifest organic heart disease, as more electrocardiograms are usually taken on patients with heart disease than on those without.

A diversity of pathologic conditions was present in the patients of this group. Eleven of the fifty-one patients had pneumonia, but in only one of them was there demonstrable fluid in the pleural cavity. There were eight cases of neoplasm, usually in the terminal stages. In two of the eight there was a pericardial or pleural effusion. There were six cases of hypothyroidism. Of these, three were definitely instances of myxedema. Rheumatic fever accounted for five cases. Low voltage usually occurred at the peak of an acute exacerbation. There were four cases of severe anemia, in two of which general anasarca was present.



These five conditions—pneumonia, neoplasm, hypothyroidism, rheumatic fever and severe anemia—account for thirty-four of the fifty-one cases (67 per cent)

The remaining seventeen cases may be disposed of briefly: polyserositis, three cases, pulmonary tuberculosis, three, bronchial asthma, two, polycythemia, one, chronic deforming arthritis, one, "gastro-enteritis," two, diabetic acidosis, one, cirrhosis of the liver with ascites, one, dermatitis medicamentosa, one, undiagnosed, one, fever of unknown origin, one

On summarizing this group of fifty-one cases, it is found that in thirty-nine (76 per cent) there was no evidence of edema, ascites or pericardial or pleural effusion. The absence was often corroborated at autopsy. In the remaining twelve cases (24 per cent) an excess of fluid was present in one of the serous cavities or as edema.

It is, of course, impossible to say that all the patients in this "non-cardiac" group were free from organic heart disease. All that can be said is that this group was free from symptoms or physical signs pointing to cardiac disease and that, in those cases in which autopsies were performed, no evidence of pathologic changes in the heart could be found.

#### THE SIGNIFICANCE OF LOW VOLTAGE IN PATIENTS WITHOUT OBVIOUS HEART DISEASE

It would be foolhardy to attempt to draw conclusions from such a small series, especially in view of the fact that the cases must be subdivided according to diagnosis into even smaller groups.

The six patients with hypothyroidism were all living at the last report. In these cases it is probable that the appearance of low voltage was due to a local change in the skin itself and not to an altered cardiac function.

Two of the four patients with severe anemia had anasarca. These two patients were alive and in good condition one and a half and four years, respectively, after low voltage was detected in the electrocardiogram. The other two patients did not show even slight edema of the ankles, yet low voltage was present. These patients were alive after eight months and four years, respectively. Apparently, the appearance of the electrocardiographic abnormality was of no significance.

In contrast to the two preceding subgroups were the eight cases of neoplasm. The eight patients died, as might be expected from the nature of their disease. One patient survived for two and a half months after the electrocardiogram showed low voltage. The average duration of life for the group, however, was four weeks. Nothing of the Q-R-S group was present in the records of four of these patients, and auricular

fibrillation was observed once. In one patient a hydropericardium secondary to metastatic involvement of the pericardium was found at autopsy. A second case showed no edema or effusions and the heart was normal at autopsy.

The group with rheumatic fever is of some interest. All five patients were alive at the last report. In four cases low voltage was present on admission, at a time when the disease was most acute, and disappeared with the subsidence of symptoms and signs of activity. In three of these four there was also prolongation of the P-R interval, which disappeared with improvement in the patient's condition. The fifth patient had an essentially normal electrocardiogram at first, but low voltage developed during a flare-up of the rheumatic process. As in the other four cases, low voltage was again a transient anomaly. It is tempting to speculate that in these five patients with rheumatic fever the occurrence of low voltage was in some way connected with the exudative phenomena present during acute episodes of the disease process.

The seventeen miscellaneous cases considered together as one group are too few to analyze satisfactorily. Thirteen patients were living when last heard of. One patient with polyserositis died three years after discharge. The patient whose condition was undiagnosed died two weeks after the electrocardiogram was taken, and aside from necrosis of the liver nothing could be found at autopsy to account for death. The heart was normal. Two of the three patients with pulmonary tuberculosis died. In one of these death occurred in another hospital several months after transfer. In the other, death occurred on the same day that the electrocardiogram was taken. Death was the result of a miliary dissemination. No edema was present, nor was there an abnormal amount of free fluid in the serous cavities. The heart was normal.

In the foregoing forty cases it appears that the finding of low voltage in the electrocardiogram was not of much significance. Sometimes it was associated with edema, hydropericardium, ascites or pleural effusion. In other instances, as in the neoplasm group, it seemed to occur in a cachectic state, which may be assumed to have included the myocardium.

There remain to be considered the eleven patients with pneumonia. In ten of these patients there was no evidence of edema, empyema, pleural effusion or involvement of the pericardium. One patient had both empyema and purulent pericarditis and died with a terminal septicemia. It may be of significance that six (55 per cent) of the eleven patients died, which is a considerably higher mortality rate than that of patients with pneumonia as a group. Autopsies were performed on

three patients. Two of the cases showed no excess of free fluid in the pericardial or pleural cavities, and in both the heart was normal. In the third case, already alluded to, there were empyema and suppurative pericarditis. Although this series is small, it seems that the occurrence of low voltage in the electrocardiograms of patients with pneumonia may be of serious prognostic import.

#### THE SIGNIFICANCE OF LOW VOLTAGE IN PATIENTS WITH CARDIAC DISEASE

In an attempt to attain a closer approximation of the significance of low voltage appearing in the electrocardiograms of patients with heart disease a "control" group of patients with heart disease was selected for purposes of comparison with the group with low voltage. One hundred patients with heart disease but without low voltage in the electrocardiograms were chosen as controls. The only basis for selec-

TABLE 1—*Comparison of the Control Group with the Low Voltage Group*

Etiology	Control Group	Low Voltage Group
Arteriosclerotic	67%	67% (76 cases)
Rheumatic	27%	25% (28 cases)
Syphilitic	6%	6% (7 cases)
Miscellaneous	0%	2% (2 cases)
	100%	100%
Average age	50 years	53 years
Presence of cardiac insufficiency (congestive)	55%	56%
Presence of other electrocardiographic abnormalities	73%	80% (90 cases)

tion was a temporal one. For example, ten patients (9 per cent) of the low voltage group entered the hospital in 1925. To make the control series comparable, 9 per cent of the patients for this series were accordingly selected from the files for 1925, and so on for each of the ten years included in this survey.

That the two groups are comparable in addition to the time relationships may be seen from table 1.

*Comparison of Mortality Rates*—For the Two Entire Groups. No follow-up data were obtained for twenty-three patients in the group of 113 with low voltage in the electrocardiogram. Of the remaining ninety patients, fifty (56 per cent) were known to be dead within an average period of ninety-two days, while forty patients (44 per cent) were known to be alive after an average of thirteen and one-half months. In the control group of a hundred cases it was possible to follow ninety-eight. Of the ninety-eight patients for whom some follow-up reports were obtained, sixty-nine (70 per cent) were alive after an average of twenty months, while twenty-nine (30 per cent) were dead after an average of one year and nine months.

The results may be summarized as follows

Low voltage group (90 cases)

Alive, 44% in 13½ months  
Dead, 56% in 3 months

Control group (98 cases)

Alive, 70% in 20 months  
Dead, 30% in 21 months

By Age Groups Ninety-eight cases in the control series were arranged by decades and compared with the ninety cases showing low

TABLE 2—*Comparison of Mortality by Age Groups*

Decade	Group	Total Cases	Living			Dead		
			Number	Per centage	Average Duration of Observation in Days	Number	Per centage	Average Duration of Observation in Days
0 9 yrs	Low voltage	1	0			1	100	60
	Control	0						
10 19 yrs	Low voltage	3	0			3	100	7
	Control	14	7	50	741	7	50	720
20 29 yrs	Low voltage	1	0			1	100	1
	Control	4	3	75	893	1	25	20
30 39 yrs	Low voltage	11	6	55	310	5	45	195
	Control	7	5	71	350	2	29	820
40 49 yrs	Low voltage	21	10	48	450	11	52	67
	Control	23	19	83	637	4	17	818
50 59 yrs	Low voltage	29	16	55	355	13	45	174
	Control	29	19	66	549	10	34	398
60 69 yrs	Low voltage	17	6	35	675	11	65	60
	Control	15	13	87	615	2	13	143
70 79 yrs	Low voltage	7	2	29	203	5	71	49
	Control	6	3	50	607	3	50	1,388

TABLE 3—*Comparison of the Mortality According to Etiologic Groups*

Etiology	Group	Total Cases	No Fol low Up	Cases Fol lowed	Num ber Living	Per cent age Alive	Average Duration of Observation in Days	Num ber Dead	Per cent age Dead	Average Duration of Observation in Days
Arterio sclerotic	Low voltage	76	16	60	32	53	410	28	47	119
	Control	67	2	65	47	72	532	18	28	536
Rheumatic	Low voltage	28	6	22	6	27	485	16	73	83
	Control	27	0	27	18	67	898	9	33	605
Syphilitic	Low voltage	7	1	6	1	17	210	5	83	46
	Control	6	0	6	4	67	60	2	33	76
Miscellaneous	Low voltage	2	0	2	1	50	240	1	50	60
	Control	0								

voltage The results may be seen in table 2 In this table the term "average duration of observation" refers to the average duration of the period of observation in the follow-up clinic in the group of living patients or the duration of observation before death in those cases in which the patients were known to have died

It will be noted that the mortality of the patients who showed low voltage in their electrocardiograms was greater in all decades than the controls, and that the period of observation before death was shorter

in each case. Among the patients who were still alive, the difference in duration of the periods of observation for the two groups was less striking, but in only one instance (the decade from 60 to 69 years) was this period greater in the low voltage group than in the controls.

**By Etiologic Groups.** The mortality of the patients showing low voltage was greater than that of the controls in each of the three main groups of heart disease, as seen in table 3. The difference was least marked in patients with arteriosclerotic heart disease. It was striking, however, in both the rheumatic and the syphilitic group, in which the mortality in the low voltage series was 73 and 83 per cent, respectively, as compared to 33 per cent in each instance in the control group.

TABLE 4—*Mortality in Groups With and Without Congestive Failure*

Congestive Failure	Group	Total Cases	No Fol low Up	Cases Fol lowed	Num ber Living	Per cent age Alive	Average Duration of Obser vation in Days	Num ber Dead	Per cent age Dead	Average Duration of Obser vation in Days
Present	Low voltage	63	11	52	22	42	452	30	58	121
	Control	55	0	55	34	62	620	21	38	477
Absent	Low voltage	43	12	31	15	48	406	16	52	80
	Control	45	2	43	35	81	784	8	19	828

TABLE 5—*Comparison of the Mortality in Groups With and Without Other Electrocardiographic Abnormalities*

Electro cardio graphic Abnor malities	Group	Total Cases	No Fol low Up	Cases Fol lowed	Num ber Living	Per cent age Alive	Average Duration of Obser vation in Days	Num ber Dead	Per cent age Dead	Average Duration of Obser vation in Days
Present	Low voltage	90	16	74	36	49	427	38	51	129
	Control	73	1	72	48	67	570	24	33	413
Absent	Low voltage	23	7	16	3	19	160	13	81	49
	Control	27	1	26	24	92	561	2	8	180

**According to the Presence or Absence of Congestive Failure.** In the group of patients with low voltage in the electrocardiogram it will be recalled that sixty-three had edema, ascites, hydrothorax or pericardial effusion, while in forty-three cases there was no evidence of abnormal accumulation of fluid. In addition there were seven cases that could not be put successfully into either group. It becomes apparent from a study of table 4 that the mortality is greater both in the presence or in the absence of congestive failure when low voltage is present in the electrocardiogram than in the control group without low voltage.

**According to the Presence or Absence of Other Electrocardiographic Abnormalities.** In 80 per cent of the group of cases showing low voltage in the electrocardiogram other abnormalities were present such as auricular fibrillation, inversion of T<sub>1</sub> or T<sub>2</sub>, block (both auriculo-

ventricular and intraventricular) or marked deformity of the Q-R-S group. Similar abnormalities were present in 73 per cent of the control group. In table 5 the comparisons are summarized. Regardless of the presence or absence of other electrocardiographic abnormalities, the mortality is greater in the low voltage group than in the control series. A point of interest is the greater mortality in the cases with low voltage in which low voltage was the only significant change in the record. Perhaps this is a statistical artefact, but, in this small series at least, it would appear that the prognosis is grave when low voltage is an isolated finding.

#### SUMMARY AND CONCLUSIONS

- 1 The records of 164 patients who have shown low voltage in their electrocardiograms have been analyzed.
- 2 One hundred and thirteen patients had manifest heart disease. In the remaining fifty-one cases without apparent cardiac involvement, a variety of diseases was present.
- 3 In the group with heart disease, low voltage appeared to be related to the presence of congestive failure in sixty-three cases, but congestive failure was absent in forty-three cases, and seven cases could not be classified.
- 4 In the group of patients without heart disease, an abnormal accumulation of fluid was present in thirty-nine cases and absent in twelve cases.
- 5 The significance of low voltage in patients without obvious heart disease is not clear. It is suggested that its occurrence in pneumonia is of serious prognostic import.
- 6 In patients with heart disease low voltage appears to be of considerable prognostic significance. In comparison with a control group the mortality was greater within a shorter period of observation in the low voltage group. This was true regardless of age, type of heart disease, presence or absence of congestive failure and presence or absence of other electrocardiographic abnormalities.

# TREATMENT OF ADDISON'S DISEASE WITH CORTIN (HARTMAN)

REPORT OF FOUR CASES

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That substitution treatment of Addison's disease is not yet fully developed at first thought seems surprising. It is certainly not Addison's fault. In 1855 he not only described the disease but demonstrated its cause. This was seventeen years before Sir William Gull, his colleague at Guy's Hospital, merely described myxedema, and twenty-seven years before Kochei and Reverdin showed that myxedema is due to lack of thyroid tissue. In spite of this later start, myxedema is now easily treated with replacement therapy, while Addison's disease remains a problem. The knowledge concerning replacement therapy in other later described endocrine deficiencies, such as diabetes and parathyroid tetany, has likewise passed far beyond that in Addison's disease.

Just as progress of knowledge in Addison's disease has been slow, so is evaluation of treatment difficult, and for the same reason. Science, in the final analysis, depends on measurements. No measuring stick has been found for insufficiency of the supra-renal cortex. The worker in this field looks with envy at the determinations of blood calcium, blood sugar and basal metabolism, which serve as measuring sticks in other fields of endocrinology. The experimenter in insufficiency of the supra-renal cortex has had to rely almost entirely on the cumbersome measuring stick furnished by prevention of death in adrenalectomized animals. Indeed the one physiologic fact that can be stated with certainty regarding the hormone of the supra-renal cortex, which was first demonstrated in 1856 by Brown-Sequard (a former member of the staff of this hospital, who was appointed to the Board of Consultants of the Massachusetts General Hospital in 1864), is that it is necessary for life.

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From the medical services of the Massachusetts General Hospital

In spite of this handicap, extracts have been prepared that will prolong life in adrenalectomized animals,<sup>1</sup> and there are now extracts that will keep adrenalectomized animals alive indefinitely.<sup>2</sup> These extracts have been found to be of value in the treatment of patients with Addison's disease.<sup>3</sup> This paper deals with the treatment of four patients with Addison's disease by means of Hartman's extract, cortin.

Before presenting the data, we wish to point out that clinical evidence is always largely circumstantial. This is especially true in regard to Addison's disease, because of the lack of a delicate measuring stick and the tendency to spontaneous remissions. The evidence that we shall present is admittedly largely circumstantial. Such evidence, if based on enough observations, should constitute proof. We believe, in case 4, moreover, that we have evidence that is more than circumstantial.

The preparation of cortin used in all of our cases was supplied by Dr. Frank A. Hartman and shipped to Boston from Buffalo. In this paper the dosage is expressed in cubic centimeters. Each cubic centimeter represents the extract of 50 Gm. of adrenal cortex. The usual daily dosage was from 16 to 20 cc. administered subcutaneously in four divided doses.

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## REPORT OF CASES

*CASE 1*—A 30 year old white married man, with active pulmonary tuberculosis, with extreme weakness and generalized pigmentation of six months' duration and with low blood pressure, showed marked symptomatic improvement when cortin was given in conjunction with fluids and dextrose by intravenous injection. He died seven days after treatment was discontinued.

*History*—Albert D., a 30 year old white married man, entered the hospital on March 31, 1931, complaining of weakness and epigastric pain of one year's duration, and was discharged on May 24, 1931. He died on May 31, 1931.

One year before admission epigastric pain and nausea had developed. The pain was dull and radiated both to the right and to the left. At about the same time the patient began to notice weakness, fatigability, somnolence, dizziness and pigmentation of the skin. Five months after the onset of the illness he was forced to stop work on account of weakness. The pigmentation continued to increase, as did other symptoms. He lost 17 pounds (7.7 Kg.) in weight.

The patient's past history revealed that he had had pleurisy for two weeks at the age of 18.

*Physical Examination*—Examination showed a young man of medium stature with evidence of recent loss of weight. There was marked pigmentation of the skin and the buccal mucous membrane. The lungs were clear at the time of admission. The blood pressure was 92 systolic and 70 diastolic.

The results of laboratory tests were as follows. The Hinton test<sup>4</sup> was negative. The urine, red blood cell count, hemoglobin, white blood cell count and smear were within normal limits. The stool was normal. The sputum was positive for tubercle bacilli. The basal metabolic rate was minus 2. The blood sugar was 121 mg. per hundred cubic centimeters; the blood nonprotein nitrogen was 44 mg., and the blood cholesterol, 104 mg. The electrocardiogram showed slight right axis deviation. Roentgen examination of the chest showed coarse mottled dulness involving both apices and the first interspaces. No roentgenographic evidence of calcification of the suprarenals was found.

*Course of Illness*—After seven days of treatment, with the administration of a total of 98 cc. of cortin subcutaneously and 30 cc. of cortin intravenously and fluids in five intravenous injections of from 200 to 450 cc. each, the patient showed the following improvement: (1) disappearance of nausea and vomiting, (2) restoration of fair appetite and (3) increase of strength.

After eight more days of treatment, with a total of 152 cc. more of cortin administered subcutaneously, the patient's condition was remarkably good in every respect and he was eating with relish three meals daily. He continued to do well for twenty days following the institution of treatment. He then began to lose strength, and on the thirty-seventh day of treatment nausea and vomiting began again. This was temporarily controlled by an intravenous injection of 600 cc. of 10 per cent dextrose. The temperature, which at first had tended to be subnormal, rose to febrile levels. Many rales appeared over both pulmonary fields. Roentgen examination of the chest showed extension of the pulmonary process. It was decided that the patient would die of pulmonary tuberculosis even if the Addison's disease were controlled. A massive dose of cortin was given which arrested the nausea and vomiting. Treatment with cortin was then stopped, and the situation was explained to the family. The patient was taken home. He lived only one week after substitution therapy was discontinued. The patient lost 16 pounds (7.3 Kg.) during his fifty-five days in the hospital. Treatment was without effect.

4 A serologic test for syphilis.

on the nonprotein nitrogen of the blood, which varied between 33 and 44 mg per hundred cubic centimeters, or on the blood sugar, which varied between 121 and 144 mg per hundred cubic centimeters. The blood cholesterol three days before discharge had sunk to 44 mg per hundred cubic centimeters. The massive dose of cortin was given on that day, and on the following two days the cholesterol content was 83 and 89 mg, respectively.

*Comment*—The evidence of the efficacy of the substitution treatment in this case rests on the disappearance of nausea and vomiting and the restitution of appetite and euphoria with the institution of treatment and on the shortness of the period of survival following the cessation of treatment. The evidence remains circumstantial, because other forms of treatment, the intravenous injection of dextrose especially, were used together with cortin.

*CASE 2*—A widow, aged 62, with recent onset of weakness, slight pigmentation and mild hypotension and with evidence of quiescent pulmonary tuberculosis, showed symptomatic improvement when the administration of cortin was added to other forms of treatment. Observations made during a nine day period of withdrawal of cortin are compared with similar observations during fore-periods and after-periods of administration of cortin.

*History*—Mrs. A. D. W., a widow, aged 62, was admitted to the New England Baptist Hospital, complaining of weakness, in March, 1931, where the diagnosis of Addison's disease was made by Dr. Albert Hornor. She was discharged on May 12, 1931, and was studied at the Massachusetts General Hospital in July 1931.

Weakness and fatigability developed in January, 1931, four months prior to the institution of treatment. In April, 1931, nausea, vomiting, increase in pigmentation and low blood pressure appeared while the patient was under observation at the Baptist Hospital. Two years prior to the onset of these symptoms diabetes had suddenly developed. Concomitant with the onset of the symptoms of Addison's disease, the patient's tolerance for carbohydrate had risen so that she was now able to eat candy and other rich carbohydrate foods without the occurrence of glycosuria.

The past history revealed a mild chronic diarrhea of nineteen years' duration, ending in 1930. There had been pneumonia, followed by eight months of convalescence, in 1893, and hemoptysis on four occasions, from 1910 to 1920. Operations included hemorrhoidectomy in 1903 and tonsillectomy in 1927. Menstruation had always been scanty. The menopause had occurred at the age of 45. Before the onset of diabetes the patient weighed 152 pounds (68.9 Kg), and afterward she weighed 139 pounds (63 Kg). At the onset of the weakness, in January, 1931, she weighed 128 pounds (58.1 Kg) and seven months later, 110 pounds (49.9 Kg).

*Physical Examination*—Examination on July 7, 1931, showed a well developed but poorly nourished woman. There were patchy pigmentation of the skin and slight purplish pigmentation of the tongue. There was enlargement of the left submaxillary glands, which were probably tuberculous. The blood pressure varied between 74 and 155 systolic and 55 and 100 diastolic during the period of observation. Râles were recorded at times at the apexes of both lungs, but a diagnosis of active pulmonary tuberculosis was not made. There were hypertrophic changes in the finger joints.

Laboratory tests showed The urine was normal The red blood cell count was 3,780,000, hemoglobin (Sahli), 77 per cent, the white blood cell count, 10,650, and the blood smear normal The stool was normal Roentgen examination showed hypertrophic changes in the joints, two calcified glands near the crest of the right ilium, diffuse mottled dulness at the apexes of both lungs and a small round area of calcification near the upper pole of the right kidney, thought to be a calcified gland rather than a calcification of the right suprarenal The electrocardiogram showed low T waves in all leads, it was not affected by the administration of cortin

*Course of Illness*—Following an intravenous injection of gallbladder dye at the New England Baptist Hospital on April 10, marked weakness, nausea and vomiting developed The patient could take no food by mouth, and she steadily lost in strength Thirteen days after the onset of these gastro-intestinal symptoms, a patch of brown pigment appeared on the left side of the nose, and there was an increase in the already slight brownish pigmentation of the face, hands and legs The patient continued to lose ground in spite of daily intravenous injections of 1,500 cc of physiologic solution of sodium chloride reinforced with 50 Gm of dextrose These injections were commenced on April 12, two days after the onset of acute symptoms The blood pressure dropped steadily from 120 systolic and 80 diastolic to 90 systolic and 60 diastolic, and the diagnosis was clear

Twenty-seven days following the onset of nausea and vomiting the administration of cortin was begun Four days later the patient began to eat, and her strength improved enough to allow her to sit up Nausea and vomiting disappeared, but recurred on several occasions when the administration of cortin was stopped or the dosage was much lowered Thus, on one occasion injections of cortin were replaced by injections of solution of sodium chloride for two days without the patient's knowledge, on the third day she was "weepy," and nausea and vomiting had recurred These symptoms were promptly relieved by resumption of the administration of cortin The degree of pigmentation was not definitely altered After thirty-six days of treatment with cortin, the patient was discharged to her home, where she continued to receive cortin and to do well

In July, 1931, the patient entered the ward for special research of the Massachusetts General Hospital for detailed studies The plan was to make careful observations during a fore-period of administration of cortin, then during an experimental period with no cortin, and finally during an after-period with cortin The data are given in table 1 During the period of withdrawal of cortin symptoms of acute insufficiency failed to develop, but the patient's appetite and euphoria were diminished, and she became generally weaker The blood pressure fell, and rose again when treatment was resumed The standing systolic pressure dropped from an average of 116 to an average of 87 mm of mercury for the last five days of the period in which no cortin was given By the sixth day after the reinstitution of treatment the systolic pressure had risen only slightly, to 94 mm of mercury, but during the following forty-three days it continued to rise and reached an average value of 130 mm of mercury Similarly the standing pulse pressure decreased from the preliminary average figure of 31 to 18, and with treatment again rose to 22 and later to 29 mm of mercury The weight dropped from 49.4 to 48.5 Kg and rose again to 49.4 Kg The caloric intake dropped from 1,818 calories daily to 1,670 calories, but continued to fall during the five days when the patient was under observation in the hospital after the reinstitution of treatment Later, on September 1 and 2, 145 cc of cortin was given in addition to the usual 20 cc daily On September 3, there was the most amazing improvement, chiefly in appetite and in spirits, and for fifteen days thereafter the appetite was voracious for three hearty meals daily The determinations in the fasting blood are interest-

TABLE 1—Data for Case 2 Showing Effect of Withdrawal of Contin on Certain Variables

[illegible]

ing only in that they show practically no changes. The blood sugar rose slightly during the period with no cortin and fell the same amount with the reinstitution of treatment. The nonprotein nitrogen, creatinine, cholesterol and chlorides of the blood were not affected. Likewise the basal metabolic rate and the urinary excretion of creatine and creatinine were unaltered. The ergograph tracings belied the clinical impression and showed a steady improvement. Thus the work done rose in the three successive periods from 23 to 32 to 34 kilogrammeters. This rise we attribute to practice rather than to improvement.

At the time of writing, eight months after the institution of treatment, the patient is still receiving cortin. She goes driving, entertains guests at tea and, on the whole, finds life pleasurable.

*Comment*—The evidence of the efficacy of substitution treatment in this case rests on the disappearance of nausea and vomiting when cortin was added to other forms of treatment that the patient was already receiving, on the many months without a relapse when she was receiving cortin daily, on the recurrence of symptoms when cortin was withdrawn and on the decrease of blood pressure when cortin was omitted.

*CASE 3*—In a 17 year old school girl of Italian descent, with arrested pulmonary tuberculosis and calcification in the suprarenal gland on one side revealed by roentgen examination, with a history of weakness for four years, acute suprarenal insufficiency developed. She was rescued from this complication by means of treatment that included cortin. Observations made during a four month period of treatment with cortin are compared with similar observations after the withdrawal of cortin.

*History*—Della D. was admitted to the Massachusetts General Hospital on April 6, 1931, complaining of weakness and pigmentation, and discharged to Johns Hopkins Hospital on Oct. 24, 1931.

Increasing pigmentation was noted four years before admission and had continued ever since. At the time of admission the patient was as dark as an East Indian. For the past five years she had been undernourished, and for three years she had been under the supervision of the board of health. Marked weakness and fatigue had been noted for only one year. A slightly productive cough developed shortly before her entrance to the hospital.

The mother had been "cured" of tuberculosis ten years before. The patient's past history included diphtheria and pertussis. The patient was treated, five years before admission, at the Reading Sanatorium for tuberculosis of the hilus.

*Physical Examination*—Examination showed undernourishment, marked pigmentation of the entire skin and patches of pigmentation on the tongue and the buccal mucous membranes. The blood pressure was 98 systolic and 65 diastolic while the patient was lying down and 80 systolic and 60 diastolic while standing.

Laboratory studies showed. The Hinton test was negative. The urine, red blood cell count, white blood cell count and smear were within normal limits. The basal metabolic rate was minus 12 and minus 18. The sputum was negative for tuberculosis. Roentgen examination showed definite calcification in the region of the left suprarenal gland, increase in width and density of the pulmonary roots and mottling in the first and second left interspaces.

*Course of Illness*—Eight days after admission the patient suddenly lost her appetite, became nauseated and vomited. She became critically ill. Her temperature first sank below normal and then rose to 103 F. The pulse rate rose to 120,

and the blood pressure dropped from 15 to 20 points. All forms of therapy were administered, including moderate doses of cortin and intravenous injections of dextrose, and the patient recovered. The blood pressure, however, remained low. Two weeks later, in spite of a daily dose of 16 cc of cortin, a subnormal temperature (96 F by mouth) developed, which was again followed by a high temperature (101.6 F) and collapse. Again intravenous injection of dextrose was resorted to, and large doses of cortin were administered. Again the patient made a miraculous recovery. Cortin, from 20 to 24 cc daily, was continued for three months without further mishap. The systolic pressure vacillated around 80 mm of mercury. The patient lost 2.3 Kg in weight. The pigmentation remained unchanged. She was able to walk around the premises. After these three months of treatment, cortin was omitted in order to study the effect of withdrawal on certain variable factors. During the next two and a half months the patient received no cortin and did well. She gained 5.3 Kg. The most significant change was a definite increase in the tendency to subnormal temperatures. During this period the basal metabolism varied from minus 2 to minus 28 (it was from minus 16 to minus 24 during the treatment with cortin), the fasting blood sugar varied from 66 to 84 mg per hundred cubic centimeters (it was 67 and 81 mg during treatment with cortin), the blood nonprotein nitrogen varied from 20 to 25 mg per hundred cubic centimeters (it was 24 and 26 mg during treatment with cortin), and the ergographic records remained about the same. The blood cholesterol requires special comment. It was 127 and 124 mg per hundred cubic centimeters during treatment with cortin. The level on the whole was not affected by withdrawal of cortin. Thus, two weeks after withdrawal the blood cholesterol was 128 mg. About three weeks after withdrawal, however, the level was found one morning to be 367 mg. The serum at this time was lipemic. Two days later the level was 138 mg. No explanation for this sudden rise was found.

*Comment*—The evidence of the efficacy of treatment in this patient rests on her rescue twice from a state of acute suprarenal insufficiency concomitant with treatment with cortin. The evidence remains circumstantial again, because other forms of therapy for collapse were employed. The fact that both acute episodes were preceded by subnormal temperatures is interesting, as adrenalectomized animals are very susceptible to low temperatures. The lessened tendency to subnormal temperature during the administration of cortin is also noteworthy and is again in agreement with the results of animal experimentation.

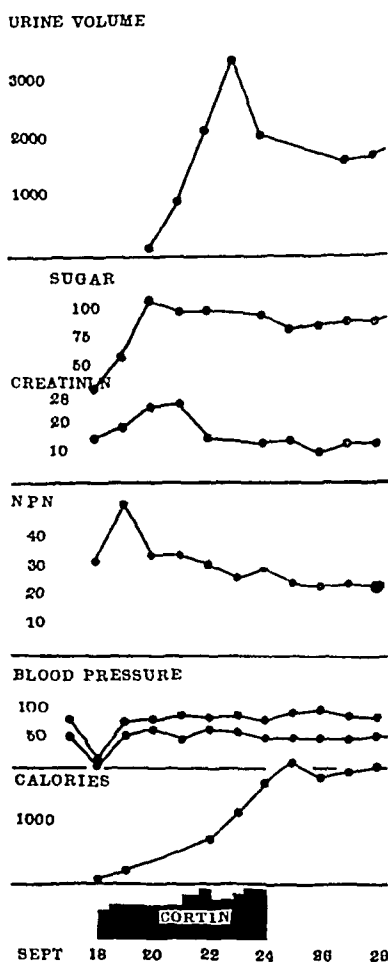
*CASE 4*—A 36 year old housewife with asthemia and hypotension of several years' duration and pigmentation of several months' duration, with no evidence of tuberculosis and a negative tuberculin test, went into a state of acute suprarenal insufficiency. By means of cortin alone she was revived from a moribund condition.

*History*—Rose M. C., a 36 year old married woman, entered the Massachusetts General Hospital for the fourth time on Aug. 19, 1931, complaining of weakness, and was discharged to the Johns Hopkins Hospital on Oct. 28, 1931.

Weakness had been present for three and one-half years at the time of her first admission in 1927. At that time the tendency to remissions of the condition was commented on, and this has characterized the later history. An erroneous diagnosis of myasthenia gravis was made on the first admission, because muscles

supplied by cranial nerves were especially involved. This aspect of the illness was not present on later entries. One month before the last admission weakness became so great that the patient was confined to an existence in bed and chair. Pigmentation, though described as "diffuse brownish" at her second admission in 1927, was minimal until one month before the fourth admission. Nausea had been present at varying intervals. It had been especially marked during the month before the last admission, during which the patient had lost 8 pounds (3.6 Kg.).

Until the fourth admission, attention had been focused on a condition probably unrelated to Addison's disease, namely, a mediastinal tumor. This tumor was situated in the region of the left auricle, was smooth in outline, had not changed



Graphic representation of the effect of cortin on certain variables in case 4

in size during the four years of observation and was not affected by roentgen irradiation. By bronchoscopy it was shown to be pressing on the left descending bronchus. To this growth were attributed the recurring attacks of bronchitis and the signs in the lower lobe of the left lung. The patient had a productive cough on admission.

At the age of 10 years the patient had had a cervical abscess, which was opened and drained. She had had nocturia "all her life." The history of catamenia was normal.

*Physical Examination*—Examination showed a poorly nourished woman with diffuse, marked, brownish pigmentation, including patches of pigmentation on the tongue. The heart was normal, except for an enlarged supracardiac dulness (per-

haps caused by the tumor) The blood pressure was 90 systolic and 60 diastolic (it had been 95 systolic and 65 diastolic on her first admission) The chest showed signs at the base of the left lung consistent with localized chronic pulmonary infection due to bronchial compression

Laboratory studies showed The Hinton test was negative The urine, red blood cell count, white blood cell count and blood smear showed nothing remarkable Roentgen examination of the suprarenals revealed no calcification The tuberculin tests with a dilution of 1:10,000 (human and bovine) were negative at forty-eight hours Gastric analysis showed no free hydrochloric acid while fasting or after the injection of ergamin

*Course of Illness*—After one month in the hospital with nonspecific treatment, the patient had a sudden severe turn for the worse On September 17, nausea and vomiting, tachycardia and circulatory collapse developed By the following afternoon the patient had sunk into a state of extreme suprarenal insufficiency The blood pressure was 40 systolic The pulse rate was rapid and could not be determined at the wrist The arms and legs, in spite of a rectal temperature of 99.2 F, were icy cold, as in dying persons The patient was oliguric and dehydrated The consensus was that she would die within a few hours The sensorium was relatively clear, considering the condition The situation seemed so hopeless that the question as to whether the limited supply of cortin should or should not be used was raised However, it was decided to make use of large doses of cortin with the addition of none of the usual adjuncts to treatment, such as fluids given intravenously in the form of solutions of dextrose or sodium chloride

The effect of treatment was almost miraculous The details are shown in table 2 and the chart Six hours after the first injection the patient was able to drink orange juice and was beginning to move around in bed The heart rate had slowed from 135 to 120 The pulse could be felt at the wrist at intervals The extremities were warmer Within fifteen hours the patient became almost euphoric, could take fluids easily by mouth and had a pulse rate of 106 The blood pressure could be obtained again, and was 70 systolic and 52 diastolic Improvement continued By the fourth day a craving for saltine crackers developed (table 2, on chlorides), and by the sixth day the patient's appetite had become voracious Double vision, which had been present, disappeared on the fifth day Headaches, which the patient had had daily for a year, disappeared for ten days following treatment

The changes in the chemical composition of the blood resulting from treatment with cortin are shown in the chart The blood sugar rose from 35 to 111 mg per hundred cubic centimeters in forty-eight hours As the urinary secretion rose, the high nonprotein nitrogen and creatinine levels of the blood fell

*Comment*—The insidious onset, the negative tuberculin tests and the absence of apical lesions suggest that this patient was suffering from the type of Addison's disease with atrophy of the suprarenal cortex We believe that the evidence of the efficacy of treatment in this patient is more than circumstantial Except for cortin, all forms of treatment known to be of value in acute collapse from suprarenal insufficiency were withheld With cortin alone the patient recovered Insulin in diabetic coma is no more convincing than cortin was in this case Having been rescued from acute collapse, the patient maintained the good condition induced without further treatment with cortin, thus showing that the suprarenals had power to recover This observation has been reported by others<sup>35</sup>





## COMMENT

Certain individual points in agreement and certain in disagreement with other writers have appeared from the studies reported. We found the same definite changes in the unmeasurable clinical symptomatology noted in the clinical studies with the Swingle and Pfiffner preparation,<sup>3f</sup> namely, (1) "disappearance of anorexia, nausea, and vomiting, and reappearance of appetite," (2) "relief from fatigue and increase in strength and endurance" and (3) "change in the mental attitude characterized by hope and euphoria." Although the effect of cortin on the appetite was striking, none of our four patients actually gained in weight under treatment.

When one turns to the triad of objective features, asthenia, hypotension, and pigmentation, the findings are less clearcut.

*Encephalographic Tracings*—Careful tracings were done on the patients while under observation. A priori one would think this might furnish the desired "measuring stick." The results were disappointing. The tracings failed to fluctuate with the patient's condition and were often surprisingly little affected by cortin. Practice and mental attitude are factors that are difficult to control. Thus the patient in case 2 continued to improve as regards the work done, when the evidence as a whole pointed to a general decrease in strength.

*Blood Pressure*—When a patient is recovering from a state of shock the blood pressure rises from the extreme low level as a result of the administration of cortin. But the effect of cortin on the low blood pressure in chronic suprarenal insufficiency is less striking. Only in case 2 did the blood pressure seem to respond after many days of treatment. The tendency of the blood pressure in Addison's disease to fall on standing was decreased by cortin.

*Pigmentation*—In none of our patients was pigmentation unequivocally decreased. In case 2 it was definitely increased under treatment. A lessening in pigmentation has been reported for the Swingle and Pfiffner preparation<sup>5</sup> and for cortin.<sup>3c</sup> The discrepancy may be due, of course, to difference in extracts, difference in dosage or difference in patients.

*Blood Cholesterol*—Influenced by the work of Reiss,<sup>6</sup> we followed the blood cholesterol value carefully. This author suggested that the hormone of the suprarenal cortex in conjunction with the reticulo-endothelial system fixes cholesterol from the blood into the tissues, and he reported a lowering of the blood cholesterol as a result of the administration of extract of active suprarenal cortex. Rogoff and

5 Rowntree et al (footnote 3, f) Simpson (footnote 3, g)

6 Reiss, M. Studien über die Funktion der Nebennierenrinde. III. Nebennierenrinde und Cholesterinstoffwechsel, *Endokrinologie* 7 1, 1930

Stewart,<sup>7</sup> on the other hand, found no constant change in the blood cholesterol in adrenalectomized dogs. Our data are interesting but inconsistent. The patient in case 1 had a low blood cholesterol value, which was increased from 44 to 86 mg per hundred cubic centimeters after a large injection of cortin. The patient in case 2, who had almost daily determinations of blood cholesterol during periods of administration and withdrawal of the hormone, showed an almost constant level. Of ten determinations, the minimum value was 184 mg per hundred cubic centimeters and the maximum 195 mg. In the patient in case 3 an interesting isolated observation was made. One morning during the third week following the discontinuation of cortin the serum was found to be lipemic, and the blood cholesterol was 367 mg per hundred cubic centimeters, the previous level having been 120 mg. There was no change in the patient's condition, there had been no change in her diet and the blood cholesterol on the following day was 138 mg. A similar less striking episode occurred in case 4.

*Nonprotein Nitrogen*—A lowering of the blood nonprotein nitrogen and creatinine by cortin during acute insufficiency was demonstrated in case 4. This is in agreement with results in animal experimentation. But as measuring sticks these quantities are of value only when the patient is moribund. These values were not affected by cortin in case 2.

*Blood Sugar*—In agreement with the results of other investigators the blood sugar, when low, rose after the injection of cortin (from 35 mg to 111 mg per hundred cubic centimeters in case 4), but when normal it was unaffected by cortin (case 3). The average blood sugar during fasting in case 2 (table) rose during the period of withdrawal of cortin from 95 mg to 126 mg per hundred cubic centimeters and fell, after treatment was reestablished, to 95 mg. But the significance of the latter change is further complicated by the fact that this patient in the past had suffered from diabetes.

*Basal Metabolism*—In no one of our patients was the basal metabolism strikingly low, and cortin was without effect on it.

*Electrocardiograms*—Clinical observation and animal experimentation indicate that the hormone of the suprarenal cortex is intimately related to the mechanism of muscular contraction. The low blood pressure and weak pulse of acute suprarenal insufficiency force one to the conclusion that the strength of the ventricular contraction is lessened in this condition. One might suppose that the electrocardiogram would reveal small complexes during states of acute suprarenal

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<sup>7</sup> Rogoff, J. M., and Stewart, G. N. Studies on Adrenal Insufficiency. VII. Further Blood Studies (Cholesterol and Calcium) in Control Adrenalectomized Dogs, *Am J Physiol* **86**: 25, 1928.

insufficiency and larger complexes during recovery. In case 4, the electrocardiograms showed no significant variations, as the patient was revived from a state of circulatory collapse and as the pulse and blood pressure rose from almost imperceptible levels to fair strength. The complexes increased in size, but the variations were within the limits of error. In two other cases the electrocardiogram was studied with and without treatment with cortin and no significant variations were found.

*Temperature Charts*—Hartman<sup>8</sup> has shown that adrenalectomized rats have less resistance to cold temperatures than do normal rats or adrenalectomized rats treated with cortin. Untreated adrenalectomized rats will show, when placed in a cold environment, a drop in temperature as great as 10 C., and may die following the adventure. Under precisely the same conditions, normal rats or adrenalectomized rats treated with cortin will show a drop of only 2 C. In all probability the suprarenals influence body temperature through the medium of the skeletal muscles. Cold temperatures throw a strain on the heat-regulating mechanism, possibly on the suprarenal cortex. Hartman<sup>9</sup> has demonstrated hypertrophy of the adrenals in normal rats following exposure to such temperatures. In the same manner lowering of the body temperature in cases of Addison's disease might cause additional strain on the residual cortical tissue with resulting relapses. The observations made in cases 3 and 4 seem to bear this out. Both the acute episodes in case 3 and the single acute episode in case 4 were preceded by subnormal temperatures. One cannot say from the data whether the sequence was exposure, subnormal temperature, increased load on the suprarenal cortex and precipitation of acute insufficiency, or whether a subnormal temperature may not be the first indication of insufficiency. The additional observation made in case 3, that the tendency to subnormal temperatures disappeared under treatment with cortin, is likewise in agreement with the results of animal experimentation and is very suggestive. Indeed, a resistance of body temperature to lowering of temperature on exposure may some day be made into that much-to-be-desired clinical measuring stick of suprarenal insufficiency.

The most convincing observations that have resulted from our studies, as regards the benefit of cortin to the patient, were those related to the treatment of the acute collapse of suprarenal insufficiency and the ability of two of our patients so treated to go for long periods without further substitution treatment. One receives the impression

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<sup>8</sup> Hartman, F. A. Increased Resistance to Cold Produced by Cortin After Adrenalectomy, *Proc Soc Exper Biol & Med* 28:702, 1931.

<sup>9</sup> Hartman. Personal communication.

that in a patient with perhaps mild chronic suprarenal insufficiency a vicious cycle is set up, for some unknown reason (perhaps exposure to cold), which leads to collapse, and that cortin can break up this cycle. Once the cycle is interrupted the patient may for a considerable period be relatively symptom-free. When the patient with Addison's disease is not having acute symptoms, the efficacy of cortin in the doses employed is less dramatic.

#### SUMMARY AND CONCLUSIONS

1 Four patients with Addison's disease have been treated with cortin (Haitman's extract). Of these, three were in all likelihood suffering from tuberculosis of the suprarenal glands and one from primary atrophy of the suprarenal cortex. We believe that all the patients received benefit from treatment.

2 A scientific evaluation of the efficacy of treatment is curtailed by the absence of a chemical or physical variable that fluctuates proportionately to the degree of suprarenal insufficiency, and that can be accurately measured.

3 The clinical evaluation of the efficacy of treatment rests chiefly on the following factors: (*a*) disappearance of nausea and vomiting, (*b*) restoration of appetite, (*c*) increase in strength and feeling of well-being and (*d*) prevention of death in acute suprarenal insufficiency (this is the most important).

4 In one patient with acute suprarenal insufficiency in a moribund condition, the administration of cortin alone, without any adjuncts to treatment, produced a dramatic result. The nonprotein nitrogen of the blood was reduced to normal, and the blood sugar was elevated to normal, concomitant with treatment.

5 The effect of cortin on ergographic tracings, blood pressure, pigmentation, blood cholesterol, blood nonprotein nitrogen, blood creatinine, blood sugar, urinary excretion of creatine and creatinine, the basal metabolic rate and electrocardiographic tracings has been studied and discussed. None of these possible variables has been found of value in the following of the fluctuations in the degree of suprarenal insufficiency.

6 The tendency to subnormal temperature was decreased by treatment with cortin. It was further noted that three acute episodes of suprarenal insufficiency were ushered in by subnormal temperatures. The subnormal temperatures may have been the cause or the result of the insufficiency.

7 Cortin has proved of the most value in the treatment of patients who are in a prostrate and moribund condition. Thus in the clinic as in the laboratory the best measuring stick of its efficacy remains the test of life or death.

## ADDENDUM

Since this paper was submitted for publication, two more in this group of four patients have died. Only one of the group is still living. A brief summary of the subsequent clinical data and the autopsy observations for these two patients is of importance.

CASE 2 (Mrs. A. D. W.)—After a year of successful treatment with cortin, severe local reactions began to develop in February, 1932, and on February 27 cortin was discontinued. After a brief latent period the patient began to show renewed evidence of suprarenal insufficiency, and in a few days nausea, vomiting and increased pigmentation had developed. A marked stiffness of the hamstring muscles, especially on the left, developed, which suggested localized tetanus. Cortin was given intravenously, and tetanus antitoxin was given intravenously as well as intraspinally. The patient failed to respond to treatment and died on March 9. Her blood pressure was exceedingly well maintained throughout the illness, which at one time made the diagnosis seem questionable. On the day of death the blood pressure was 118 systolic and 80 diastolic. Autopsy revealed tuberculosis of both suprarenals with complete destruction of the glands. Gross and microscopic examination revealed no remaining normal suprarenal tissue.

CASE 4 (Rose M. C.)—The patient was transferred to the Johns Hopkins Hospital on October 28, 1931. Shortly after arriving at Baltimore, she had several successive relapses during which she was treated successfully by extract of the adrenal cortex. Jaundice developed on November 9 and increased steadily. Secondary anemia, bleeding from the gums, edema of the lips and ascites appeared, and the patient died on Dec. 29, 1931. Autopsy revealed Addison's disease of the so-called "cortical atrophy" type, with almost complete destruction of the medulla of both suprarenals.

The trustees of the Massachusetts General Hospital, on behalf of the patients and in the interest of science, put a considerable sum of money at the authors' disposal to help defray the cost of the production of cortin. Dr. Frank A. Hartman, although his limited facilities were taxed to the utmost, met our emergencies as they arose and curtailed his own scientific investigations in order to spare cortin for our patients.

# PERICARDITIS

## IV FIBRINOUS PERICARDITIS AND "SOLDIER'S PATCHES"

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AND

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Fibrinous pericarditis without effusion is undoubtedly the most common disease of the pericardium. It is the forerunner of many cases of pericarditis with effusion, of purulent pericarditis, and of adherent pericarditis. The uncomplicated form of this disease is probably the most innocuous form of pericarditis. The inflammatory process may involve either the visceral or the parietal layers of the pericardium, or both, and may be localized or widespread in its involvement. A fibrinous exudate occurs, which, when the deposition is marked, results in the "shaggy" or "bread and butter" appearance of the pericardium.

### MATERIAL

Fibrinous pericarditis without effusion occurred in sixty-two of 373 cases of pericarditis, an incidence of 16.6 per cent.

These cases occurred in forty-three males (69.4 per cent) and nineteen females (30.6 per cent). It is interesting to observe that the incidence of cases of pericarditis of all groups in males is predominant. The reason for this is not clear.

Virtually all decades of life were represented. There were two patients in the first decade of life, four in the second, five in the third, eight in the fourth, seven in the fifth, sixteen in the sixth, thirteen in the seventh, and seven in the eighth. The youngest patient was only 4 months of age, whereas the oldest was 74 years of age. The average age was 48.2 years. The majority of patients (70.9 per cent) were between the thirtieth and the seventieth year of life.

### ETIOLOGY

Intrathoracic infection appeared to be causative of fibrinous pericarditis in thirty-three cases (53.2 per cent). Primary pericarditis of indeterminate bacterial type occurred next in frequency, in twelve cases (19.4 per cent). Rheumatic fever was the apparent cause in nine cases (14.5 per cent), and infection elsewhere in the body in eight cases (12.9

per cent) Infection, therefore, was the basis of the pericarditis in the majority of instances

The intrathoracic infections were as follows pneumonia in fourteen cases (42.4 per cent), empyema in eleven cases (33.3 per cent), pulmonary abscess in four cases (12.1 per cent), pleuritis in two cases (6.1 per cent) and pulmonary tuberculosis in two cases (6.1 per cent)

In all cases in which fibrinous pericarditis was associated with rheumatic heart disease, it seemed justifiable to conclude that rheumatic fever was the etiologic condition

The cases classed as primary pericarditis occurred in the absence of infection elsewhere in the body and were believed to be examples of direct invasion of the pericardium Nine cases were associated with recent or healed cardiac infarction

The cases of fibrinous pericarditis that resulted from infection elsewhere in the body than the thorax comprised four cases of generalized peritonitis three cases of pyelonephritis, and one case of perforated gastric ulcer

#### PATHOLOGY

The weights of the hearts in forty-seven cases (75.8 per cent) were available for study Two cases were excluded because the patients were children The average cardiac weight was 409.6 Gm The smallest heart weighed 200 Gm, whereas the greatest recorded cardiac weight was 793 Gm The average weight is considerably greater than that of the normal heart as shown by the studies of Smith,<sup>1</sup> the average normal adult heart of the male weighs 294 Gm, and the average normal heart of the female, 250 Gm In eleven cases (23.4 per cent) the weight of the heart was between 200 and 299 Gm Thirty-six patients (76.6 per cent) had cardiac weights in excess of 300 Gm, as follows fifteen (31.9 per cent), between 300 and 399 Gm, eight (17.0 per cent), between 400 and 499 Gm nine (19.2 per cent), between 500 and 599 Gm, one (2.1 per cent), between 600 and 699 Gm, and three (6.4 per cent), between 700 and 799 Gm

The averages are materially influenced by the inclusion of cases with associated cardiac disease, lesions dominant in their influence on cardiac hypertrophy These cases will be discussed separately in the ensuing text

*Associated Cardiac Disease*—Associated disease of the heart occurred in thirty-one cases (50 per cent) This incidence closely approximates that of associated cardiac disease in cases of adherent pericarditis (53.5 per cent), and greatly exceeds that in cases of pericarditis with effusion (29.2 per cent)

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<sup>1</sup> Smith, H. L. The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age, *Am Heart J* 4:79 (Oct) 1928



Hypertensive cardiac disease occurred with greatest frequency, it was recorded in eleven cases (17.7 per cent). Among these cases, the average cardiac weight was 555.2 Gm, the smallest, 381 Gm, and the greatest, 793 Gm. The youngest patient was only 18 years of age, the oldest, 72. The average age was 47.9 years.

Coronary disease occurred in ten cases (16.2 per cent) and included nine cases of recent or healed cardiac infarction. The average cardiac weight was 463 Gm. The minimal cardiac weight was 300 Gm, whereas the maximal weight was 709 Gm. Four patients had associated hypertension, with their exclusion, the average weight was 411.6 Gm. The youngest patient was 50 years of age, the oldest, 74. The average age was 64.8 years.

Rheumatic heart disease occurred in eight cases (12.9 per cent). The involvement of valves, with the frequency, was as follows: mitral, three cases, mitral and aortic, three cases, mitral and tricuspid, two cases, and mitral, aortic and tricuspid, one case. The average cardiac weight was 397 Gm, the smallest was 283 Gm, and the largest, 615 Gm. The age of the youngest patient was 6 years, that of the oldest, 52. The average age was 28.3 years.

Subacute bacterial endocarditis (*Streptococcus viridans*) occurred in two cases (3.2 per cent), in both instances engrafted on an old mitral lesion. The average cardiac weight was 517.5 Gm, the hearts weighing 505 and 530 Gm, respectively. The patients were 16 and 33 years of age, the average age, then, was 24.5 years.

The average weight of the heart in all cases in which there was associated cardiac disease was 496.3 Gm.

*Fibinous Pericarditis Without Associated Cardiac Disease*—Thirty-one of the cases (50 per cent) were in this subgroup. In these cases, the influence of lesions other than fibinous pericarditis on cardiac hypertrophy has been eliminated. The average cardiac weight was 251.9 Gm, indicating that the average heart in this group is normal in weight. The smallest heart weighed 200 Gm, whereas the largest weighed 460 Gm. The youngest patient was only 4 months of age, whereas the oldest was 73 years of age. The average age was 49.7 years, almost approximating that of the patients with associated cardiac disease, the latter were an average of 2.9 years younger.

*Pleural Fluid*—Fluid appeared in one or both pleural cavities in twenty-two cases (35.4 per cent). The fluid was confined to the right pleural cavity in nine cases and to the left in six cases, it was contained in both in seven cases. It was purulent in eleven cases, exudative in two cases, and transudative in nine cases.

#### CLINICAL FEATURES

Forty-two patients (67.8 per cent) presented complaints entirely unrelated to the cardiovascular system: carcinoma, six cases, nephritis

and pneumonia, three cases, respectively, cholecystitis, gangrenous appendicitis, hernia, adenomatous goiter, empyema and benign prostatic hypertrophy, each two cases, and vesical calculus, renal calculus, perinephritic abscess, hypernephroma, erythema multiforme, calculus of the common bile duct, miliary tuberculosis, pulmonary tuberculosis, cellulitis of the neck, fracture of the femur, Addison's disease, pulmonary abscess, bronchiectasis, subdiaphragmatic abscess, duodenal ulcer, staphylococcal pyemia, fecal fistula and arsenical poisoning, each one case

The remaining twenty patients (32.3 per cent) of the sixty-two with fibrinous pericarditis presented complaints directly related to the heart. They all had associated cardiac disease and comprised 64.5 per cent of the group of thirty-one patients who had such associated disease.

The most characteristic physical sign of fibrinous pericarditis is a pericardial friction rub. It may be present but a short time, or its presence may be evanescent. Its recorded incidence in this study was 11.3 per cent.

*Electrocardiography*—Electrocardiograms of twelve patients were obtained, all of whom had associated cardiac disease, the resulting abnormalities obviously arose from the primary disease of the heart. In two cases there was incomplete bundle branch block, in five cases, significant T wave negativity, in one case, changes in the R-T segment, and in one case, auricular flutter. In three cases, the electrocardiogram was essentially unaltered.

#### MODE OF DEATH

Twenty patients (32.2 per cent) died as the result of heart failure, all had associated cardiac disease. Nine patients (14.5 per cent) died of coronary disease, their average heart weight was 326.7 Gm, and their average age was 64.2 years. Hypertensive heart disease was the cause of death in five cases (8.1 per cent), the average weight of the heart was 642 Gm, and the average age of the victims, 49 years. Four patients (6.4 per cent) with rheumatic heart disease died of congestive failure, the average weight of the heart was 428.3 Gm, and the average age, only 25.5 years. The two patients (3.2 per cent) with subacute bacterial endocarditis died of their disease, the average cardiac weight was 517.5 Gm, the average age was 24.5 years. The average weight of the hearts of the entire group of patients who died of heart disease was 526 Gm, and the average age of the patients, 49.2 years.

The remaining forty-two patients (67.8 per cent) died of causes unrelated to the heart. Sepsis was responsible for the deaths of twenty-two, pneumonia, nine, uremia, five, pulmonary embolism, two, tuberculosis, two, Addison's disease, one, and arsenical poisoning, one. The average cardiac weight in these cases was 354.2 Gm, a value not greatly in excess of normal. The average age of the patients was 49.2 years.

## SO-CALLED SOLDIER'S PATCHES

Soldier's patches, or milk spots, are whitish, localized areas found from time to time in the pericardium. They are believed to represent relics of localized, nonobliterating pericarditis. The areas are usually fibrous, but at times hyaline changes are evident. We found records of fifteen cases in which these changes were present. The cases occurred in eleven males (73.3 per cent) and four females (26.7 per cent). The average age of the patients was 47.6 years, the youngest patient was 22 and the oldest 79 years. Only three patients had associated cardiac disease. The average weight of the heart of those without associated cardiac disease was virtually normal, 319.9 Gm. The smallest heart weighed 234 Gm, whereas the largest weighed 427 Gm. The majority of the patients (86.6 per cent) died of causes unrelated to the heart.

It is possible that the so-called soldier's patches, or milk spots, represent the scars of previous, localized, fibrinous pericarditis, but their presence does not seem in any way to interfere with the normal behavior of the heart.

## COMMENT AND SUMMARY

Sixty-two cases of fibrinous pericarditis without effusion, in which the patients came to necropsy at the Mayo Clinic, form the basis of this study. There are also comments on fifteen cases in which there were so-called soldier's patches, or milk spots. The incidence in males was greater than that in females.

Associated cardiac disease occurred in thirty-one cases (50 per cent). Although half of the patients had associated cardiac disease, only twenty had complaints fundamentally related to the cardiovascular system. In the majority of cases in which infections occurred either spontaneously or following surgical intervention, disorders unrelated to the heart were present. The predominant clinical features in 32.2 per cent of the cases were referable to the heart. The remaining cases represented a miscellaneous group of diseases. Death from cardiac disease occurred in 32.3 per cent of the cases. In the remaining cases, death was from causes unrelated to the heart.

The weights of the hearts in forty-seven cases were available for study and are discussed.

The major subject of consideration in the etiology of fibrinous pericarditis, as one would anticipate, is an infectious process.

Fibrinous pericarditis appears to be the simplest and most innocuous form of pericarditis. It seems to be prodromal to more serious forms of pericarditis, namely, pericarditis with effusion in some cases, purulent pericarditis in others, and adherent pericarditis in many cases in which the patient survives the etiologic disease.

# PERICARDITIS

## V TERMINAL PERICARDITIS

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AND

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For many years pathologists have recognized a form of pericarditis which afflicts patients who are dying of debilitating diseases, but which does not appear to be concerned in their deaths. This has been designated "terminal pericarditis."

In considering pericarditis we have attempted to separate our material into groups conforming to pathologic and clinical criteria, so that comparative study would be possible. We appreciate the fact that separation into clearcut types is often difficult, and that some degree of overlapping may occur. We have attempted to show that fibrinous pericarditis without effusion is the simplest form of pericarditis, but have stated that it usually is the forerunner of purulent or of nonpurulent pericarditis with effusion, and of adherent pericarditis.

The accurate segregation of cases of so-called terminal pericarditis is obviously difficult, for it is possible to include cases of fibrinous pericarditis. In order to minimize the possibility of error, we selected, for inclusion in the group of cases of terminal pericarditis, only those in which there was no evidence of healing, in contrast to those placed in the group of fibrinous pericarditis, in which definite attempt at repair was evident. Unfortunately, we cannot report on the bacteriology of these cases at this time, for a separate study by one of our associates<sup>1</sup> has not been concluded. Thus far, it appears that cultures invariably yield negative results.

### MATERIAL

In previous studies of this series it has been pointed out that records of 373 cases of pericarditis have been found among records of 8,912 postmortem examinations performed at the Mayo Clinic. Forty cases of terminal pericarditis were found, an incidence of 0.4 per cent in the entire number, and of 10.7 per cent in cases of pericarditis. As with all forms of pericarditis, there were more male than female patients. There were twenty-eight males (70 per cent) and twelve females (30

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From the Section on Cardiology, the Mayo Clinic

<sup>1</sup> Work carried on by Dr. H. J. Kullman

per cent) The youngest patient was 15 years of age, the oldest, 83 The average age was 48.7 years Only 7.5 per cent of the patients were aged less than 30 years

#### PATHOLOGIC DATA

The weights of the hearts in twenty-nine cases (72.5 per cent) were available for study The average cardiac weight was 377.3 Gm, the smallest, 250 Gm, and the largest, 650 Gm In twenty-three cases (57.3 per cent) the weight of the heart exceeded 300 Gm

*Associated Cardiac Disease*—There was a high incidence of associated cardiac disease, twenty-one cases (52.5 per cent), although the heart was predominantly a factor in the clinical syndrome in only four cases.

Hypertensive cardiac disease occurred with greatest frequency, thirteen cases (32.5 per cent) The average weight of the heart was 434.2 Gm The smallest heart weighed 345 Gm, whereas the largest heart weighed 623 Gm The average age of these patients was 46.1 years, the youngest patient was 22 years of age, and the oldest, 66

Coronary disease occurred in three cases (7.5 per cent) The weight of the heart was recorded in only one case, 385 Gm The average age of these patients was 64.3 years

Rheumatic heart disease was present in three cases (7.5 per cent), mitral stenosis occurred in two of these cases and marked aortic stenosis in one The average cardiac weight was 525 Gm, and the average age was 42.3 years

There was one case (2.5 per cent) of subacute bacterial endocarditis (*Streptococcus viridans*), the original lesion in which was mitral stenosis The heart weighed 450 Gm, and the patient was 46 years of age

One case (2.5 per cent) of hyperthyroid heart disease occurred The heart weighed 350 Gm, and the patient was only 15 years of age

The average weight of the heart in all cases in which there was associated cardiac disease was 438.2 Gm

*Terminal Pericarditis Without Associated Cardiac Disease*—There were nineteen cases (47.5 per cent) in which there was no associated cardiac pathologic condition The average weight of the heart in this group was 302.3 Gm The smallest heart weighed 250 Gm, and the largest, 400 Gm Thus, the difference in average cardiac weight between the groups of patients with associated cardiac disease, and those without, was 135.9 Gm

#### CLINICAL FEATURES

The major diagnosis in thirteen cases (32.5 per cent) was carcinoma, in the majority of these cases there was metastasis, or extension of the malignant process to contiguous structures The site of

carcinoma was as follows stomach, three cases, colon, two cases, bladder, two cases, and esophagus, breast, lung, uterine cervix, larynx and anterior thoracic wall (recurrence), one case each

Nephritis occurred in ten cases (25 per cent), the majority of the patients died of uremia

Hyperthyroidism occurred in four cases (10 per cent), these included two cases of exophthalmic goiter and two cases of hyperfunctioning adenomatous goiter There were two cases with prostatic hypertrophy The other diagnoses were pneumonia, pulmonary abscess, Addison's disease, subacute bacterial endocarditis (*Streptococcus viridans*), esophageal diverticulum, gastrocolic fistula, cellulitis of the leg, pernicious anemia, septicemia, uterine fibromyoma and rheumatic heart disease with aortic stenosis, each in one case

Although the primary diseases in cases in which terminal pericarditis occurred cover a wide range, carcinoma and nephritis together comprised 57.5 per cent

Infections occurred in twenty cases (50 per cent), an incidence distinctly less than that in the other forms of pericarditis Associated intrathoracic infection occurred in twelve cases (30 per cent) and comprised pneumonia alone, seven cases, pneumonia and empyema together, two cases, and empyema alone, suppurative mediastinitis and purulent bronchitis, each one case Infections elsewhere in the body occurred in eight cases (20 per cent) and included such diseases as peritonitis, pyelonephritis, cellulitis and ulcerative colitis

#### CAUSE OF DEATH

Only four patients (10 per cent) died as the result of cardiac disease Three of these died of congestive heart failure and one of subacute bacterial endocarditis The remaining patients died of the following causes nephritis, eleven cases, pneumonia, seven cases, peritonitis, five cases, hyperthyroidism, two cases, Addison's disease, one case, pulmonary embolism, one case, ulcerative colitis, one case, and sepsis elsewhere in the body, eight cases

#### COMMENT

From this study it appears that the condition designated as terminal pericarditis in some respects does not differ materially from that seen in certain cases of acute fibrinous pericarditis Our ground for distinguishing between the two conditions has been explained Terminal pericarditis occurs with greatest frequency in cases in which the primary disease is of long standing and results in progressive debility This is particularly exemplified by the high incidence of carcinoma and nephritis That the pericarditis is noninfectious in the majority of

cases is possible, but definite proof of this is still lacking. Identification of terminal pericarditis rests almost wholly on postmortem examination.

#### SUMMARY

A condition classified as terminal pericarditis occurred in forty of 373 cases of pericarditis, an incidence of 10.7 per cent. A marked predominance of the incidence in males occurred.

Among the major clinical diagnoses in the cases comprising this group, those of carcinoma and nephritis predominated.

Associated cardiac disease occurred in twenty-one cases (52.5 per cent).

Death from heart disease occurred in only 10 per cent of the cases. In the remaining cases, 90 per cent of the patients died of causes unrelated to the heart.

Pleural fluid was present in 35.4 per cent of the cases, an accessory diagnostic sign suggesting the possibility of pericardial involvement.

# SEDIMENTATION RATE OF BLOOD CORPUSCLES IN SYNOVIAL FLUID AND IN PLASMA

METHOD OF ESTIMATION AND SIGNIFICANCE IN ARTHRITIS

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Synovial fluids show marked differences of suspension stability. Some are rendered clear by short centrifugation, while others still contain corpuscles after prolonged action of the centrifuge. This is suggestive of differences in composition, and an investigation appeared to be pertinent from a theoretical and a clinical point of view. The value of the sedimentation rate of blood corpuscles in plasma for the differential diagnosis of arthritis is limited by the interference of various factors. By simultaneous estimation in the synovial fluid, it was hoped to eliminate some nonspecific elements and to increase the diagnostic value of the sedimentation speed in arthritis. This program required a method of suspending an amount of corpuscles in synovial fluid equal to that in blood and a suitable technic for the comparative sedimentation test.

## TECHNIC

*Preparation of the Suspension of Blood Corpuscles in Synovial Fluid*—Into a graduated centrifuge tube is put 2 cc of 3.8 per cent sodium citrate solution, and then the amount is increased to 10 cc with synovial fluid. Into a second graduated centrifuge tube 3 cc of the sodium citrate solution is put, and venous blood is added to 15 cc. The amount can be reduced in the ratio of 1 part of citrate to 4 parts of synovial fluid or blood, the minimum required is 5 cc of citrated synovial fluid and 10 cc of blood, however. Six cubic centimeters of the citrated blood is then transferred to a separate test tube and centrifuged at a high speed, simultaneously with the citrated synovial fluid. After ten minutes of centrifugation, the tube containing blood is marked at the level of separation of the corpuscles from the serum. A second mark identifies the upper level of the plasma. In order to be assured that the separation of the cells and plasma is complete, I recentrifuge until there is no change in the level of the cells. The synovial fluid is centrifuged till the supernatant layer is clear. The plasma is then separated carefully from the corpuscles with a pipet, and an equal amount of centrifuged synovial fluid is substituted, to the upper mark. This procedure secures a suspension of corpuscles in synovial fluid equal to that in the citrated blood (fig 1).

*The Set-Up of the Sedimentation Test*—Two 5 cc pipets are marked at a height of 20 cm from the tip. Holes to a depth of about 5 mm are bored in large rubber stoppers (no 10).

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Read in part before the Clinical Conference of the Hospital for Joint Diseases, New York, Jan 5, 1932

\* Frederick Brown Research Fellowship, Hospital for Joint Diseases



The suspension of corpuscles in the synovial fluid and the remainder of the original citrated blood are now shaken until thoroughly mixed. Each is then drawn into a pipet to the mark and set up vertically in a rubber stopper, plasticine can be used for this purpose, if desired. At intervals of one hour, marks are made at the level of separation of the corpuscles from the clear fluid. Final readings are made in twenty-four hours (fig 2).

This method follows the Westergreen technic except for two modifications (1) citrate is accurately measured into tubes instead of being drawn into syringes, (2) the pipets are of larger caliber because of the higher viscosity of the synovial fluids. Finally, more readings were made than in the routine tests, in order to secure more data.

#### CONTROLS

In order to establish the adequacy of the technic, the following experiments were carried out:

1 In a number of cases, the sedimentation was interrupted after several hours, the corpuscles were resuspended, and the sedimentation was carried out a second time. The readings were found to be practically identical.

2 Tests were carried out with both unwashed corpuscles and corpuscles washed in saline. It was found that the sedimentation rates did not deviate, washing of the corpuscles was therefore abandoned.

3 Corpuscles from the blood of three different patients were suspended in three portions of the same synovial fluid in the ratio of 30 per cent of corpuscles to 70 per cent of fluid. The sedimentation curve showed an identical character in the different suspensions, although the single values varied. This proves that synovial fluid itself is largely responsible for the character of the sedimentation.

4 It was proved that neither centrifugation nor shaking has any marked influence on the sedimentation rate.

#### SUPPLEMENTARY TESTS

The viscosities of the citrated synovial fluid and plasma were determined in nearly all cases. A cell count, a differential count, Wassermann and gonococcus complement fixation, cultures and an estimation of the icterus index were made on each synovial fluid. A sedimentation by the standard Westergreen method was carried out on the remaining blood, and although somewhat higher values were found in the first hour in a great number of cases, the general character of the curve remained unchanged.

#### COMPARISON OF SEDIMENTATION CURVES

The determination of the normal sedimentation curve is necessary before pathologic changes are considered. It is simple to establish the sedimentation of normal blood, the amount of synovial fluid however

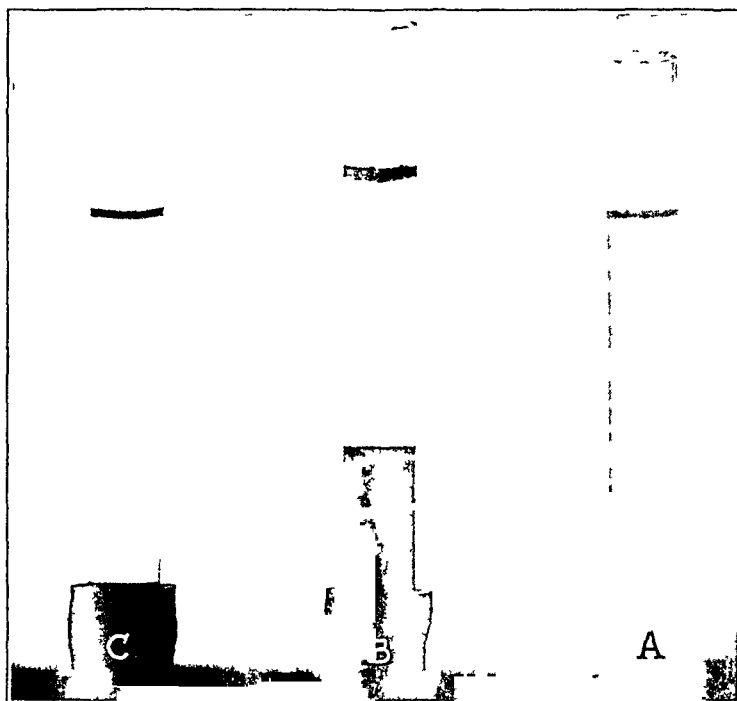


Fig 1—Preparation of blood and synovial fluid for the comparative sedimentation test *A*, centrifuged citrated blood, *B*, plasma pipetted off, with the upper and lower level marked for substitution by synovial fluid, *C*, centrifuged citrated synovial fluid

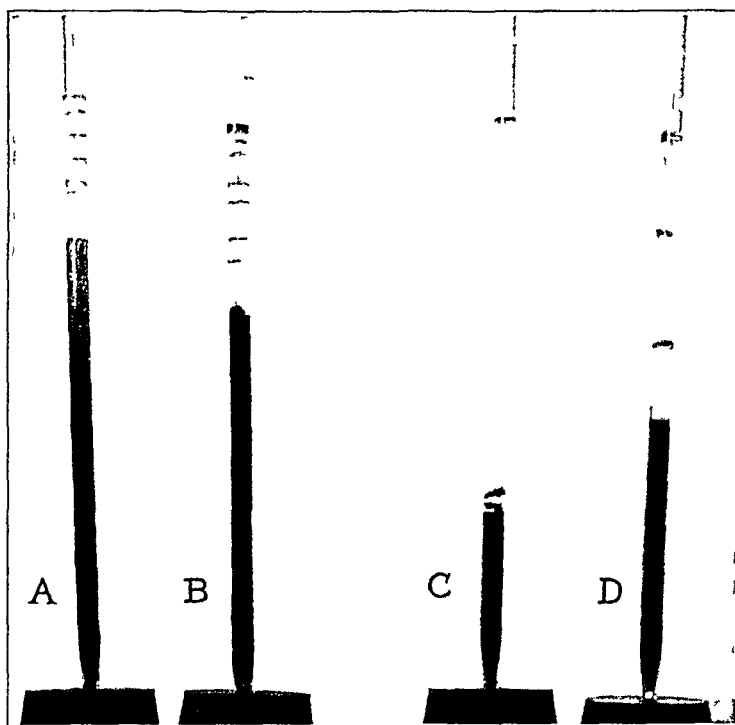


Fig 2—Comparative sedimentation of blood and synovial fluid *A* and *B*, normal sedimentation of blood (*A*) and synovial fluid (*B*) from a case of osteoarthritis *C* and *D*, highly increased sedimentation in blood (*C*) and synovial fluid (*D*) in a case of gonorrheal arthritis Each mark indicates an interval of one hour The sedimentation in twenty-four hours is shown by the column of clear fluid

in normal joints is not sufficient for the test. I have therefore substituted noninflammatory synovial effusions that showed a composition approaching the normal fluid. Figure 3 represents the average sedimentation curve in eight cases of chronic arthritis due to irritation by preceding trauma or degenerative changes of the articular surfaces (ostearthritis). The history, appearance and bacteriologic examination did not reveal an inflammatory factor, and the sedimentation of blood was normal. The synovial fluid showed a high viscosity and high mucin content, a low cell count and a prevalence of synovial lining cells, properties that preceding studies<sup>1</sup> have shown to be characteristic for normal synovial fluids. The curve of the synovial fluids shows, in comparison to that of the blood, the very slow start of the sedimentation and the

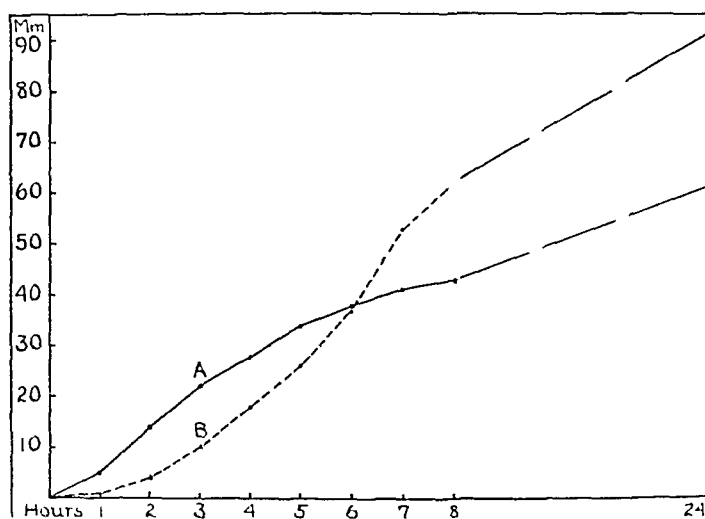


Fig 3—Standard comparative sedimentation curve, on the basis of eight cases of chronic noninflammatory (oste) arthritis. Normal blood sedimentation (A) and slow sedimentation of synovial fluid (B). The comparative sedimentation index was 526 per cent.

gradual increase after the first hour, the curve for blood is crossed after six hours. This initial delay and subsequent increase of sedimentation were observed in fifteen other noninflammatory effusions (fig 3).

The composition of normal synovial fluid explains the remarkable course of sedimentation. Synovial fluid contains a low percentage of protein, especially globulins and fibrinogen, which initiate and increase sedimentation, the start of the sedimentation is therefore slower than that in the blood. On the other hand, the mucinous substance in synovial fluid raises its viscosity far above blood plasma and probably brings about the subsequent increase of the sedimentation above that of normal blood.

<sup>1</sup> Kling, D. H. The Nature and Origin of Synovial Fluid, Arch Surg 23:543 (Oct) 1931.

## COMPARATIVE SEDIMENTATION INDEX

Westergreen and his followers consider the reading after the first hour to be the most important. By the modification outlined, the average sedimentation of normal blood in the first hour amounts to 4.75 mm, with a high normal of about 10 mm. The study of an average sedimentation curve of noninflammatory synovial fluid demonstrates that an initial delay, with an average value of 0.25 mm and a maximum of 2 mm, after the first hour, is characteristic and is produced by the composition of normal synovial fluids. The ratio of the readings after one hour for synovial fluid and plasma represents, therefore, a comparative index of the sedimentation in both fluids. This is expressed in percentage in the following formula:

Comparative sedimentation index (after one hour)

$$\frac{\text{Reading of synovial fluid}}{\text{Reading of blood}}$$

For standard curves, CSI =  $\frac{0.25}{4.75}$  or 5.26 per cent

Any change that influences the sedimentation in plasma or synovial fluid must alter this equation.

## ANALYSIS OF MATERIAL

The comparative sedimentation was carried out in sixty-one cases of arthritis, the distribution of the various types is given in table 1.

TABLE 1—*Summary of Material*

Types	Number of Cases
Acute nonspecific and gonorrheal arthritis	10
Tuberculous arthritis	2
Syphilitic arthritis	3
Chronic infectious arthritis	5
Chronic rheumatoid (atrophic) arthritis	8
Traumatic arthritis	6
Posttraumatic arthritis	13
Osteoarthritis (hypertrophic)	14
Total	61

*Acute Infectious Arthritis (Table 2)*—This group contains ten cases. The sedimentation was carried out from five days to four weeks after the onset of the condition. Eight patients had arthritis for the first time, in six cases one knee joint was involved, and in four cases, several joints. In three cases the gonorrheal etiology was established by culture, smear or gonococcus complement fixation in the synovial fluid, in two others, gonococci were found in the prostate and uterine cervix, respectively. The etiology in five cases was regarded as nonspecific, cultures and serologic tests of the joint fluids gave negative results. In these cases, the tonsils, teeth or uterus was infected, and the condition of the joints followed influenza or tonsillitis. Puerperal sepsis was responsible in one case.

The number of cells in the fluid varied from 4,880 to 120,000 per cubic centimeter, the percentage of polymorphonuclear leukocytes was from 59 to 95

The viscosity of the citrated fluid ranged from 3 to 13, and the viscosity of the citrated plasma, from 1.4 to 2.4

The average sedimentation curve for this group (fig. 4) is characterized by the high values after the first hour and by the rapid course of the sedimentation, which was almost complete after three hours in the blood and after four hours in the synovial fluid. On account of its initial high sedimentation, the curve for the blood is not crossed by that

TABLE 2—*Acute Infectious Arthritis (Nonsyphilitic and Gonorrheal)*

Case	Name	Diagnosis	Duration, Days	Sedimentation After 1 Hour		C S I,* per Cent	Vis- cosity of Fluid	Comment
				Blood	Fluid			
1	A S	Polyarthrits (?)	28	116	79	68.1	4.2	Gonococci in cervix
2	J L	Gonorrheal of right knee	5	69	45	65.2	5.4	Wassermann gonococcus complement fixation 4+, culture positive for gonococci
3	S L*	Gonorrheal of right knee	14	44	19	43.2	4.1	Smear positive for gonococci
4	S G	Septic polyarthrits	14	32	9	28.1		After puerperal fever
5	L A	Nonspecific of left knee	14	78	22	28.2		Teeth infected
6	W B	Nonspecific of right knee	7	100	25	25.0	3.0	Cervical adenitis (strep. tococci) 3 years before
7	T S	Gonorrheal of left knee	3	107	25	23.4	5.8	Gonococcus complement fixation 2+, smear positive for gonococci
8	J K	Nonspecific polyarthrits	14	108	23	21.3	4.8	Influenza
9	A W	Nonspecific of right knee	4	117	10	8.5	13.0	
10	S G	Polyarthrits (?)	7	103	7	6.8	12.8	Gonorrheal arthritis 20 years ago, gonococci in prostatic smear

\* In this and the succeeding tables, C S I indicates the comparative sedimentation index

for the synovial fluid. One exception occurred in a case of gonorrheal arthritis, in which, after two hours, the fluid registered 102 mm and the blood only 85 mm.

**Comment.** The rapid sedimentation in both blood and synovial fluid is produced by the increase of the proteins, especially fibrinogen, which in turn is caused by the inflammatory process.

Bauer and his associates<sup>2</sup> calculated the total protein content of normal synovial fluid in cattle to be 0.68 per cent, I have found, in an acute case of gonorrheal arthritis, a total protein content of 6.43 per cent, of which the globulins amounted to 4.13 per cent.

<sup>2</sup> Bauer, Walter, Bennett, G. A., Marble, Alexander, and Chaffin, Dorothy. Observations on Normal Synovial Fluid of Cattle. I. The Cellular Constituents and Nitrogen Content, *J. Exper. Med.* **52**: 835, 1930.

The sedimentation rate in the synovial fluid reflects, therefore, the degree of inflammation of the aspirated joint, while the systemic reaction determines the sedimentation speed of the blood

The comparative sedimentation index reveals the share that the local process contributes to the general reaction

In this group, the average sedimentation index is 30.3 per cent, the minimum being 6.8 per cent and the maximum 68 per cent. However, only two cases (cases 9 and 10) had a comparative sedimentation index lower than 21 per cent. The variations in the index are due to the opposite effects of the fibrinogen and mucin on the initial sedimentation, the first increases and the second decreases the initial sedimentation

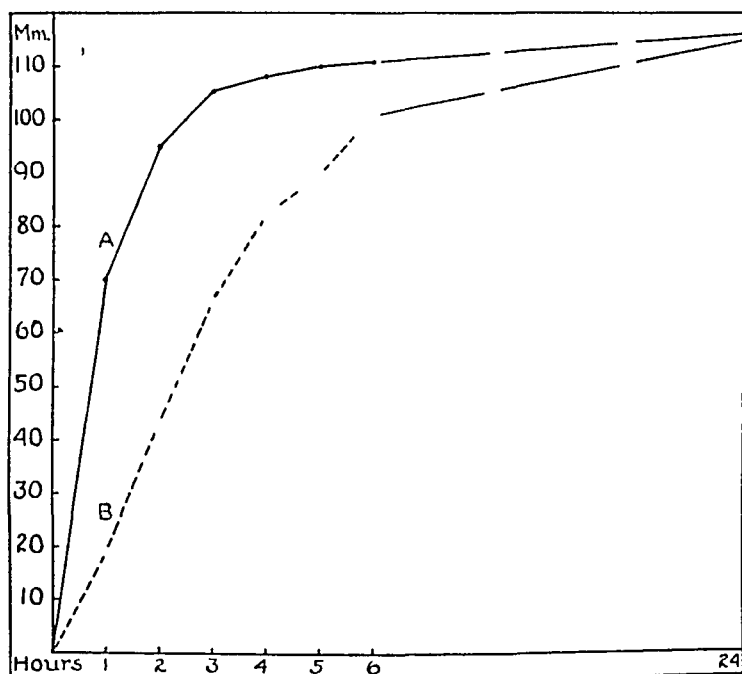


Fig 4—Average comparative sedimentation curves in ten cases of acute non-specific and gonorrheal arthritis. A is the curve for blood, and B, for synovial fluid. The comparative sedimentation index was 30.3 per cent.

speed. A low sedimentation index can therefore be produced either by a small content of protein or by a high content of mucin. The first occurs when the joint is only slightly inflamed, the second when the inflammation of the synovial membrane leads to a hypersecretion of mucinous substance.

Determination of the viscosity of the synovial fluid permits a differentiation of the causative factor of the low sedimentation index. Effusions of low protein and mucin content have also a low viscosity. Fluids with a high mucin content have a high viscosity. Cases 9 and 10 show the highest viscosity in this group. Their low sedimentation index is therefore caused by a higher content of mucin.

*Chronic Infectious Arthritis* (Table 3 and Fig 5) —This group contains five cases of monarticular arthritis. The condition of the joints followed a rectal abscess in one case and osteomyelitis in another case, in three cases no etiology other than exposure to cold was discovered. The duration of the symptoms varied from one to five years. The number of cells in the effusion varied from 4,400 to 43,000, and the percentage of polymorphonuclear leukocytes, from 18 to 88. The viscosity of the citrated fluid ranged from 5.4 to 8, the viscosity of the citrated plasma, from 1.4 to 2.1. In case 1, of five years' duration, an inert streptococcus was cultured from the synovial fluid, in the others the

TABLE 3—*Chronic Infectious Arthritis* (Nonspecific, Cases 1 to 5, Tuberculous, Cases 6 and 7, Syphilitic, Cases 8, 9 and 10)

Case	Name	Effusions	Duration	Sedimentation After 1 Hour		C S I per Cent	Vis- cosity of Fluid	Comment
				Blood	Fluid			
1	E M	Right knee	5 years	22	12	54.5	5.4	Old osteomyelitis, septicemia*
2	E P	Left knee	2 years	21	10	47.6	8.0	Syphilis latens
3	H M	Left knee	1 year	50	11	22.0		Cold after bathing
4	J R	Left knee	Indefinite	37	6	16.2	5.6	Rectal abscess 3 years ago
5	B K	Left knee	2 years	50	6	12.0	6.4	Colds
6	R G	Left knee	1½ years	59	18	30.5	5.6	Inoculation into guinea pig positive for tuberculosis
7	M G	Left knee	5 days	43	3	6.9		Inoculation into guinea pig positive for tuberculosis
8	A W	Right knee	2 years	35	19	54.3	3.2	Wassermann reaction of blood 4+, fluid 3+
9	W S	Right knee	3 weeks	13	6	46.2	16.4	Wassermann reaction of blood and fluid 3+
10	E B	Both knees	13 years	20	3	15.0	7.0	Wassermann reaction of blood and fluid 4+

\* Inert streptococci in synovial fluid

cultures were negative. All cases still showed signs of activity. The sedimentation curves show a moderate increase in the sedimentation in plasma and synovial fluid. The course of the sedimentation is gradual. In the first two cases the curve for the blood was crossed by that for the synovial fluid after three and four hours, respectively. The average comparative sedimentation index is 25 per cent, the minimum 12 per cent and the maximum 54.7 per cent. The significance of the variations of the index was fully discussed previously.

A high comparative sedimentation index in this group of monarticular arthritis indicates that the involvement of the joints is responsible for the elevation of the sedimentation of blood, a low index points to the presence of other foci. The group as a whole shows a decline of the systemic and a prevalence of the local reaction.

*Tuberculous Arthritis*—The comparative sedimentation was carried out in two cases of monarticular tuberculosis of the knee joint (table 3, cases 6 and 7) The sedimentation rates, although somewhat higher, are of the general character of those in the group of chronic infectious arthritis The comparative sedimentation index is 7 and 30 per cent, respectively

*Syphilitic Arthritis*—Three cases of monolateral and bilateral arthritis of the knee joints were diagnosed as syphilitic on the basis of positive Wassermann reactions and the roentgen and clinical findings (for data, see table 3, cases 8, 9 and 10) The sedimentation curves are somewhat lower than those in the group of chronic infectious

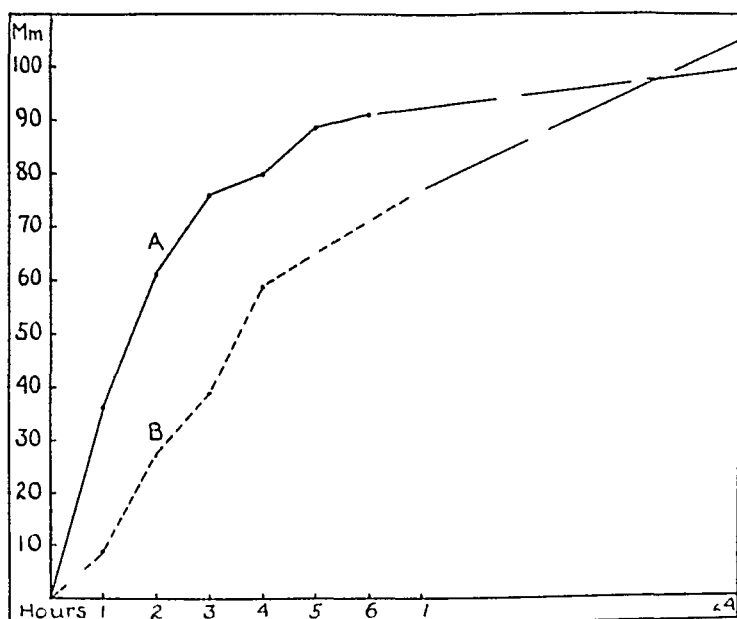


Fig 5—Average comparative sedimentation curves of the blood (A) and synovial fluid (B) in five cases of chronic infectious arthritis The comparative sedimentation index was 25 per cent

arthritis The comparative sedimentation index varies from 15 to 54 per cent Numerous investigators have found that the sedimentation rate of the blood is increased in secondary and tertiary syphilis My method demonstrated that in syphilitic arthritis the local process in the joint is probably to a large degree responsible for the increase in sedimentation

*Chronic Rheumatoid (Atrophic) Arthritis (Table 4)*—This group is represented by eight cases of polyarthritis Besides large joints, the small joints of the hands and feet were involved at an early stage, and the condition was frequently bilateral The onset was insidious and mostly before middle age The duration varied from one to twenty years No history of preceding infection was given Tonsillectomy and extraction of teeth in several cases and mastoidectomy in one case



did not check the progress. In each instance, one or more joints showed signs of active involvement. In each case, one knee joint was aspirated.

The effusions were turbid, with a cell count of from 13,200 to 34,400, and a range of polymorphonuclears from 10 to 86 per cent. Cultures, inoculations into guinea-pigs and Wassermann and gonococcus complement fixations gave negative results. The viscosity of the synovial fluids varied from 3 to 16.8, and that of the plasma from 1.3 to 2.4. The sedimentation curves are high and rank next to those in the acute cases. The comparative sedimentation index is 27.6 per cent, with a minimum of 5 per cent and a maximum of 59 per cent (fig. 6).

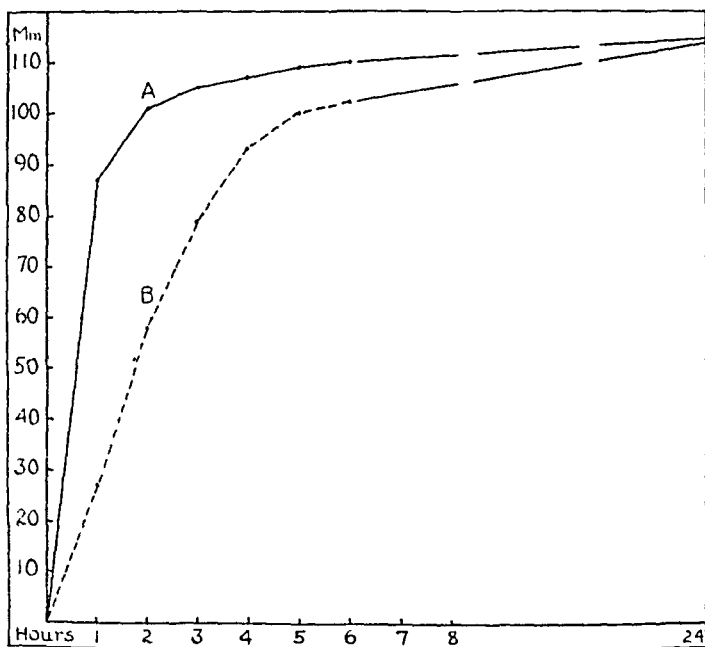


Fig. 6—Average comparative sedimentation curves of the blood (A) and synovial fluid (B) in eight cases of chronic atrophic (rheumatoid) arthritis. The comparative sedimentation rate was 27.6 per cent.

In this group of chronic, progressive polyarthritis, the sedimentation speed of the blood illustrates the general reaction and the comparative sedimentation index reflects the severity of the involvement of the aspirated joint. Case 1 showed a relatively slight increase in the sedimentation of blood, clinically, only the aspirated joint showed activity. The high comparative sedimentation index and viscosity (8.6) indicate that a combination of exudative and hypersecretory reactions is present.

The other seven cases showed a high sedimentation of blood and active involvement of several joints at the time of aspiration. In five cases, the high comparative sedimentation index indicates a severe exudative, inflammatory reaction in the aspirated joint. In two cases, a low index shows that a hypersecretory process prevails. Accordingly,

these cases (table 4, cases 7 and 8) show high viscosity due to an increase of mucin

*Traumatic Arthritis*—This group includes six cases of recent hemorrhagic effusions (table 5 and fig 7) The sedimentation rates show some increase in three cases (cases 2, 5 and 6) The average sedimentation index is 64.7 per cent, with a maximum of 183 per cent and a minimum of 34.6 per cent In none of the cases was there perfect agreement between the sedimentations in blood and fluid or in the viscosities

TABLE 4—*Chronic Rheumatoid Arthritis*

Case	Name	Diagnosis	Duration, Years	Sedimentation After 1 Hour		C S I, per Cent	Viscosity of Fluid	Age, Years
				Blood	Fluid			
1	M H	Polyarthritis	2	27	16	59.2	8.6	26
2	M B	Polyarthritis	19	67	38	56.7	7.0	29
3	H A	Polyarthritis	1	93	39	41.9	3.0	37
4	F N	Polyarthritis	20	56	15	26.8	4.4	61
5	C V	Polyarthritis	10	100	25	25.0	4.6	44
6	M B	Polyarthritis	1½	45	7	15.5	8.8	50
7	J L	Polyarthritis	8	69	9	13.0	16.0	33
8	A D	Polyarthritis	15	100	5	5.0	16.8	63

TABLE 5—*Traumatic Arthritis*

Case	Name	Diagnosis	Duration	Sedimentation After 1 Hour		C S I, per Cent	Viscosity of Fluid	Comment
				Blood	Fluid			
1	C D	Effusion of right knee	1 day	6	11	183.3	6.4	
2	M B	Effusion of left knee	2 weeks	13	14	108.0	2.2	
3	S M	Effusion of right knee	4 days	9	7	78.0	8.0	
4	H S	Avulsed fracture of right knee	2 days	6	4	66.6	6.0	
5	H T	Avulsed fracture of left knee	10 days	25	10	40.0		
6	M C	Avulsed fracture (?) of left knee	1 day	26	9	34.6	2.6	Roentgenogram negative, fat positive in synovial fluid

This indicates that even recent hemorrhagic effusions contain some component besides blood. Preceding studies on precipitation phenomena in synovial fluids<sup>1</sup> have demonstrated that almost immediately after injury irritation of the synovial membrane leads to hypersecretion and admixture of mucin to the blood.

The increase of the sedimentation of the blood in cases 5 and 6 (table 5) may be due either to some focus of infection unrelated to the injury or to an irritation due to the absorption of broken down blood. The increase in the sedimentation of the fluid, on the other hand, with the rise of the comparative sedimentation index to over 100 per cent in

cases 1 and 2 (table 5) indicates a local reaction on the basis of an increased metabolism, owing to disintegration of the blood or irritation

*Posttraumatic Arthritis* (Table 6, Fig 8)—Thirteen cases of unilateral arthritis of the knee joint were included in this group on the basis of the following criteria slight or old trauma, occupational or static strain and absence of specific or nonspecific infectious etiology Osteochondritis dissecans was found in one case, all other roentgen examinations gave negative results

The duration of the process ranged from one week to three years In five cases, the effusion showed a slight admixture of blood, in three cases, the icterus index was higher than 6 The number of white cells varied from 500 to 17,600, the percentage of polymorphonuclear leuko-

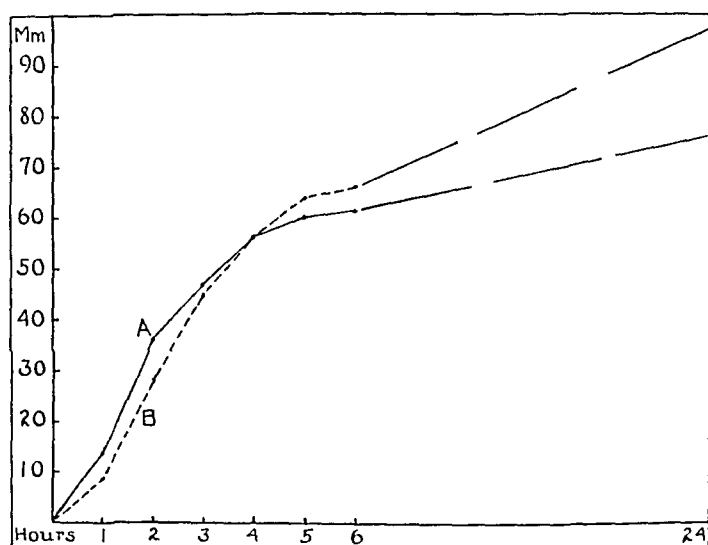


Fig 7—Average comparative sedimentation curves of the blood (A) and synovial fluid (B) in six cases of traumatic arthritis The comparative sedimentation index was 64.7 per cent

cytes, from 0 to 60 per cent, the viscosity of the fluid, from 3.7 to 23.6, and that of the blood, from 1.3 to 2 The whole group shows little systemic reaction as the sedimentation rate of the blood was normal in ten cases and only moderately increased (from 19 to 26 mm in the first hour) in three cases The sedimentation curve of the synovial fluid, on the other hand, shows the greatest variation with a comparative sedimentation index from 0 to 330 per cent

In the first three cases (table 5) the sedimentation of the fluid is higher than in the blood As in the traumatic effusions, this behavior is probably due to increased local metabolism

In five cases, the sedimentation in the blood and that in the synovial fluid almost correspond, and in two cases, the sedimentation of the synovial fluid is slow, while the viscosities are high This variation in

the sedimentation of synovial fluid in ten cases with normal sedimentation in blood is presented in figure 8

*Osteoarthritis (Hypertrophic—Table 7 and Fig 9)*—This group of fourteen patients suffered chiefly from bilateral arthritis of the knees, with deformities and pain and grating on motion. The duration ranged from several months to eight months. Roentgenograms showed osteoarthritic changes with lipping and spur formation of the articular surfaces. In one case, loose osteochondritic bodies were found in the knee joints. However, pain, swelling and effusion were more conspicuous in one joint. In seven cases, the onset of disability was recent and rather sudden, three of these patients gave a history of strain. In two cases, the effusion developed during physical therapy. The cell count varied from 200 to 32,000 per cubic millimeter, but only two cases

TABLE 6—*Posttraumatic Arthritis*

Case	Name	Effusion	Duration	Sedimentation After 1 Hour		C S I, per Cent	Vis- cosity of Fluid	Comment
				Blood	Fluid			
1	H M	Left knee	1 mo	3	10	333.3		
2	R K	Right knee	6 weeks	4	6	150.0	3.7	
3	C D	Left knee	2 mos	9	10	111.0	6.6	Occupational strain
4	S H	Right knee	1 mo	4	4	100.0	23.6	
5	I M	Left knee	1 week	6	6	100.0	5.8	Hematin particles in fluid, occupational strain
6	F M	Left knee	6 mos	6	6	100.0	9.7	
7	S S	Right knee	3 years	12	11	92.6	3.9	
8	C N	Left knee	1 year	3	2	66.6	10.0	Occupational strain
9	S R	Left knee	6 weeks	4	0	0	12.0	
10	E B	Left knee	11 days	9	0	0	15.0	Repeated falls, last 11 days previously
11	C W	Left knee	7 years	26	8	30.8	14.4	Occupational strain
12	F B	Left knee	3 years	25	6	24.0	8.0	Kicked 2 days before
13	A P	Left knee	1 week	19	3	15.8	6.0	Osteochondritis dissecans, syphilis latens

showed a count higher than 2,000. The number of polymorphonuclear leukocytes ranged from 5 to 35 per cent. In one case the fluid was slightly hemorrhagic, with an icterus index of 13, although the history did not reveal preceding trauma, in five cases, brown hematin particles were found in the fluid, which were remnants of an old hemorrhage. The viscosity of the fluid varied from 6 to 56, and that of the blood, from 1.3 to 2.2. Wassermann and gonococcus complement fixation tests gave negative results. Only one case gave a positive culture of streptococcus (table 7, case 7).

The sedimentation rate of the blood was normal in only three cases (table 7, cases 1, 2 and 3). In five cases the sedimentation in the blood was increased from 12 to 25 mm, and in seven cases, from 35 to 58 mm, after the first hour. I have found this increase in sedimentation in the blood in a large percentage of osteoarthritic cases, contrary to a number of authors who regard a normal sedimentation rate to be the rule in this condition. The value of sedimentation of the blood for differentiation of hypertrophic from infectious types is therefore

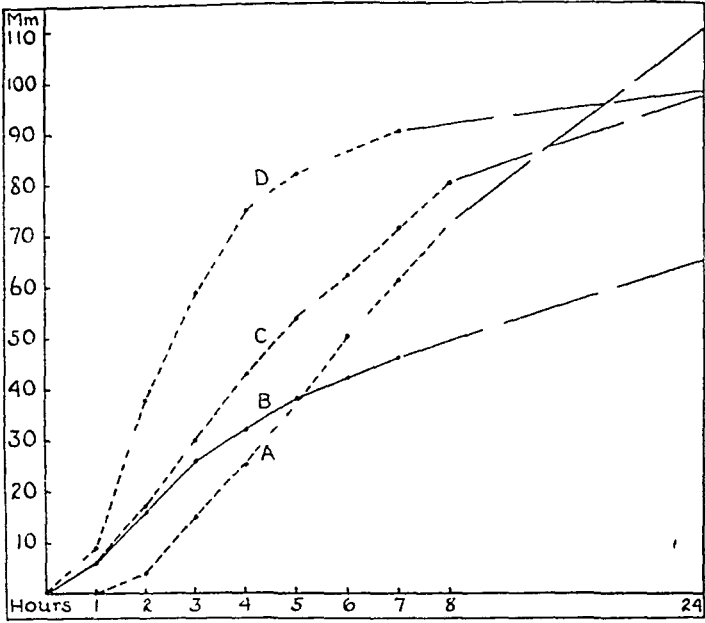


Fig 8—Variations in the sedimentation of fluid in ten cases of posttraumatic arthritis with normal sedimentation of blood *A* shows the low sedimentation of fluid in cases 9 and 10 *B* is the curve for the sedimentation of blood *C* shows the average sedimentation of fluid in cases 4, 5, 6, 7 and 8 *D* shows the high sedimentation of fluid in cases 1, 2 and 3

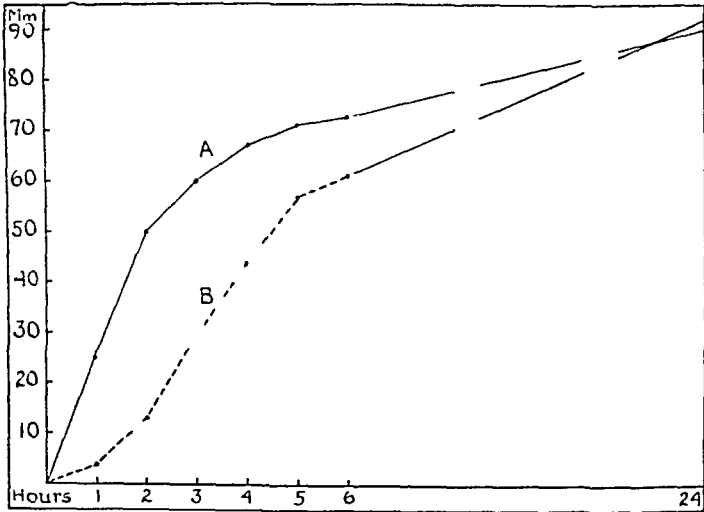


Fig 9—Average comparative sedimentation curves of the blood (*A*) and synovial fluid (*B*) in fourteen cases of osteoarthritis (hypertrophic) The comparative sedimentation index was 144 per cent

limited. The sedimentation rate in seven effusions ranged from 0 to 3 mm, and in the other half from 5 to 10 mm after one hour.

The average comparative sedimentation index was 14.4, with a minimum of 0 and a maximum of 72.7 per cent. A low comparative sedimentation index was found in this group, both with normal and with increased sedimentation in the blood. In the latter case, this indicates that the general reaction is independent of the involvement of the joints. A high sedimentation index, on the other hand, with moderate increase in sedimentation in the blood, points to the arthritic process as the main source of the reaction, due either to secondary infection (case 7, streptococcus) or to the breaking down of hematoma. Further support of this conception is the relatively low viscosity of the fluid in the cases with a high comparative sedimentation index (table 7, cases 7 and 8).

TABLE 7—*Osteoarthritis*

Case	Name	Effusion	Duration	Sedimentation After 1 Hour		C S I, per Cent	Vis- cosity of Fluid	Age, Years	Comment
				Blood	Fluid				
1	J B	Right knee	7 mos	4	0	0	40.0	44	Old psoriasis
2	L H	Right knee	?	11	0	0	48.0	45	Shipped, effusion 4 days later
3	S N	Left knee	7 yrs	12	0	0	44.0	48	
4	H H	Left knee	Uncertain	17	5	29.4	18.0	53	Effusion 2 weeks
5	R W	Right knee	2 yrs	14	5	35.7	10.8	42	Depressed arches
6	B E	Left knee	5 mos	16	6	37.5	8.6	48	Knock knees
7	R O*	Right knee	7 yrs	14	10	71.4	8.6	66	Free joint bodies effusion 2 weeks
8	N M	Right knee	2 yrs	11	8	72.7	8.0	50	Effusion 4 months
9	R A	Left knee	3 mos	25	0	0	56.0	43	
10	C P	Right knee	3 mos	35	0	0	18.0	57	Effusion after diathesis
11	S A	Right knee	5 yrs	45	2	4.4	12.4	55	
12	S S	Left knee	7 yrs	45	3	6.6	15.6	45	Effusion 1 month
13	S B	Right knee	?	47	6	10.6	13.6	50	Effusion after bak- ing 1 month
14	I H	Left knee	8 yrs	38	7	13.7	6.0	50	Injury 8 years pre- viously, frequent falls

\* Streptococcus found in both smear and culture

#### SUMMARY

In a previous study, I have demonstrated that over 90 per cent of synovial effusions have a dual composition. The systemic reaction produces extravasation of proteins and crystalloids from the circulation, the local irritation of the synovial membrane, on the other hand, leads to the secretion of a mucinous substance, which determines the physicochemical properties of the joint fluid. It produces precipitation phenomena with acids in the form of sacs and tubes, it is responsible for the high viscosity and  $p_H$  values of the synovial fluid.

The present study has revealed the antagonistic influence of the two different fractions on the suspension stability of the joint fluids. The blood proteins, especially the fibrinogen, increase, the mucin delays the initial sedimentation speed of the corpuscles in the fluid. The observation of differences in suspension stability, which prompted this investi-

gation, is therefore explained by the differences in distribution between the two components of the synovial fluid. An attempt was made to utilize this reaction for the recognition of the type and degree of involvement of the joints in different forms of arthritis.

### CONCLUSIONS

A method for the comparative estimation of the sedimentation rate of blood corpuscles in synovial fluid and plasma was developed by replacing the plasma by equal volumes of fluid.

The ratio of sedimentation of blood corpuscles in synovial fluid and plasma after one hour was found to be significant and can be expressed by the comparative sedimentation index.

On the basis of a study of sixty-one cases of arthritis by this method, the following conclusions were drawn:

The severity of an infection of the joint is indicated by the sedimentation curve in the synovial fluid, the general reaction is reflected in the blood curve.

In acute infectious polyarthritis, the comparative sedimentation index is useful in the determination of the part played by the aspirated joint within the general process.

In monarticular arthritis, a high increase in the blood sedimentation and a low sedimentation rate in the synovial fluid indicate foci of infection outside of the joint as responsible for the increase in the sedimentation in the blood.

A simultaneous determination of the sedimentation and the viscosity is helpful in differentiating the type of involvement of the joint.

Noninflammatory fluids with a low protein content have a low comparative sedimentation index and a low viscosity. This is the case in transudates. On the other hand, fluids with a high content of mucin show a low comparative sedimentation index but a high viscosity.

The differentiation of infectious from degenerative types of chronic arthritis by the sedimentation of the blood alone is not possible. The nature of the underlying process can, however, be more accurately discovered by the comparative sedimentation and the viscosity of the effusion.

NOTE—This method of comparative sedimentation was also used with other body fluids (pleural, pericardial and ascitic effusions). Four cubic centimeters of citrated blood is sufficient, as these fluids have a low viscosity. Two cubic centimeters is centrifuged, and the plasma is replaced by an equal volume of the citrated fluid to be examined. The tests are set up in the standard pipets for the Westergreen method. The findings will be reported elsewhere.

# CLINICAL SIGNIFICANCE OF ELECTROCARDIOGRAMS WITH LARGE Q WAVES IN LEAD III

THOMAS ZISKIN, M D

MINNEAPOLIS

The occurrence of a large Q wave in lead III of the electrocardiogram in certain cardiac conditions has been noted recently by some observers

Parkinson and Bedford<sup>1</sup> noted its presence in 9 of 29 patients (31 per cent) with a coronary thrombosis. In a series of 200 cases of heart disease of various types, Pardee<sup>2</sup> found 30 patients with the anginal syndrome. Of these, 8, or 27 per cent, were found to have a large Q wave in lead III. In the other 170 cases he found only 6 such records, or 3.5 per cent.

In reviewing the records of 277 normal hearts from other clinics, he found only 2 with large Q waves in lead III. He believes that this finding is closely associated with pathologic changes that involve coronary narrowing, and that the larger the Q wave in relation to the voltage of Q-R-S, the closer is this association.

Willius<sup>3</sup> reviewed approximately 70,000 electrocardiographic records at the Mayo Clinic and found 300 tracings which showed large Q waves in lead III. He stated, however, that this does not represent an accurate ratio of the incidence, owing to the fact that many tracings that previously had been considered to be essentially normal had been destroyed, and that it is possible that among these were some with large Q waves in lead III.

The majority (268, or 89.3 per cent) of the 300 records showing this sign were found in patients who had one of the following conditions: hypertensive heart disease, the anginal syndrome, hypertensive heart disease accompanied by the anginal syndrome, or arteriosclerotic

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From the Cardiac section of the United States Veterans' Hospital 106

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1 Parkinson, J, and Bedford, D. E. Successive Changes in the Electrocardiogram after Cardiac Infarction (Coronary Thrombosis), *Heart* **14** 195, 1928

2 Pardee, H. E. B. The Significance of an Electrocardiogram with a Large Q Wave in Lead III, *Arch Int Med* **46** 470 (Sept.) 1930

3 Willius, F. A. Occurrence and Significance of Electrocardiograms Displaying Large Q Waves in Lead III, *Am Heart J* **6** 723, 1931



heart disease not accompanied by the anginal syndrome or hypertension. He found only 3 cases (1 per cent) in which the heart was apparently normal.

Willius<sup>3</sup> believes that the occurrence of the large Q wave in lead III is associated with disorders in which there is a predominant strain on the left ventricle.

The present investigation is based on a study of 4,885 electrocardiograms of patients at the cardiac clinic of the United States Veterans' Hospital at Minneapolis. Eighty-six tracings, or 1.8 per cent of the entire group, were found which showed a large Q wave in lead III. The criteria set down by Pardee<sup>2</sup> were strictly adhered to in the selection of these records, namely: 1. The excursion of the Q wave in lead III must be more than 25 per cent of the greatest excursion

TABLE 1—*Correlation of Large Q Waves in Lead III with Clinical Conditions in 86 Cases*

Clinical Diagnosis	Cases	Per Cent
Coronary disease with anginal syndrome	12	14.0
Hypertension	33	38.8
Hypertension with myocardial involvement	8	9.3
Aortic insufficiency	2	2.3
Mitral stenosis	1	1.2
Ascites	2	2.3
Gas distention	1	1.2
Cardiac hypertrophy	2	2.3
Pericardial adhesions	1	1.2
Nephrosis	1	1.2
Myocardial insufficiency	3	3.4
Normal heart	20	23.2
	86	100.0

of the Q-R-S complex in any lead. 2. They must show left axis deviation of Q-R-S with  $R_1$  greater than  $R_2$  or a normal direction of the axis of Q-R-S with  $R_2$  larger than either  $R_1$  or  $R_3$ . 3. All records must show in lead III an initial downward deflection (Q) followed by a definite upward deflection (R) without an S wave. 4. Records with a downward deflection in lead III followed by an upward deflection and then another downward deflection, resembling somewhat the shape of the letter W, and also records that had somewhat the shape of a letter M were excluded.

The distribution of cases showing the large Q wave in lead III and the classification of the clinical diagnoses are shown in table 1.

It will be seen that the greatest incidence of the characteristic electrocardiographic changes occurred in the group with hypertensive heart disease, 33 of the 86 cases (38.8 per cent) being obtained in this type. This compares favorably with Willius<sup>3</sup> series, in which 40 per cent were found among the patients with hypertensive heart disease. Coronary

disease with angina pectoris was found in 12 cases (14 per cent) This is a smaller percentage than in Willius' <sup>3</sup> series, which shows 25.3 per cent with the anginal syndrome, and Pardee's <sup>2</sup> series which shows 62.8 per cent of the cases with the anginal syndrome This may be accounted for by the fact that the present study was made on a group of men, the majority of whom were in the fourth and fifth decade of life, while the other studies included persons of all ages and perhaps many more patients in the later decades

The other clinical cardiac conditions found compare favorably in distribution with both Willius' <sup>3</sup> and Pardee's <sup>2</sup> series, except for the percentage of normal hearts found

It is significant that in the present study, a large Q wave in lead III was found in 20 patients with normal hearts, or 23.2 per cent of the entire group of 86 cases, while in Pardee's <sup>2</sup> series no such cases were found, and in Willius' <sup>3</sup> series only 3 cases (1 per cent) were found in normal hearts In the composite group of electrocardiograms made from 977 normal persons in their control series, only two cases (0.2 per cent) with this characteristic electrocardiographic sign were found

The finding of so large a percentage of normal hearts in my series led to the study of other factors which might be involved in the production of the large Q wave in lead III besides those given by Pardee <sup>2</sup> and Willius <sup>3</sup> The position of the heart within the thoracic cavity, the size of the heart and the electrical axis were investigated in each case of this group and compared with a control group of an approximately equal number of cases with the same clinical diagnosis and with electrocardiograms having either a small Q wave in lead III or no Q wave at all The findings are recorded in tables 2 to 6

A significant difference in the angle of inclination of the heart was noted between the roentgenograms of the Q wave series and those of the control series The angle of inclination of the heart in the Q wave series varied from 20 to 40 degrees, the average for the entire group being 29.6 degrees One patient with mitral stenosis showed a cardiac angle of 44 degrees In the control series the angle of inclination of the heart was 40 degrees or over in the majority of the cases, the average for the entire group being 42.9 degrees There is a difference of over 13 degrees in the relative position of the heart between the Q wave series and the control series The heart tends to lie in a more horizontal position in the chest cavity in the group showing large Q waves in lead III This variation is practically constant in all of the clinical conditions studied and also in the normal hearts It must be considered, therefore, a significant factor in the causation of large Q waves in lead III

TABLE 2—*Hypertension*

Q Wave Series					Control Series			
Name	Cardio thoracic Ratio (X Ray) per Cent	Cardiac Angle (X Ray) Degrees	Electrical Axis, Degrees	Q Wave (Percentage of Greatest R Deflec tion)	Name	Cardio thoracic Ratio (X Ray) per Cent	Cardiac Angle (X Ray) Degrees	Electrical Axis, Degrees
LA	39	32	+67	33	HAP	41	47	+62
JMA	46	28	+46	83	NKR	43	46	+59
WAA	45	36	+55	45	PPM	40	42	+52
GB	44	30	+49	75	EJB	42	36	+41
AB	48	30	+58	62	JHF	43	45	+77
EEC	50	36	+59	28	LdeS	45	37	+64
AC	55	28	+51	46	FGJ	49	46	+78
VC	46	35	+47	33	WBJ	45	46	+84
ERC	42	42	+49	50	HL	45	40	+12
WD	46	33	+49	50	JAM	50	45	+69
JdeM	45	34	+50	27	JKL	49	39	+52
WAF	41	30	+76	57	HJS	45	43	+55
JF	49	31	+55	50	EPS	47	40	+52
VF	48	32	+50	33	CS	46	45	+48
JF	46	35	+58	50	JB	41	54	+73
OLH	46	31	+49	40	FDC	43	45	+67
EH	52	27	+67	33	TPY	34	56	+69
EMI	48	40	+47	66	RGV	45	44	+73
JJ	48	24	+41	33	ALS	46	46	+43
BLK	44	26	+58	47	PS	42	43	+24
OM	48	29	+45	30	WHS	44	37	+16
MMcM	48	27	+44	25	IS	41	36	—30
DMcC	47	29	+45	45	FJV	45	43	+65
SGM	46	33	+55	25	TFR	44	42	+40
FWP	43	30	+45	27	GA	41	40	+48
RCP	46	30	+69	57	SS	48	41	+55
TR	52	25	+44	25	DL	47	45	+49
JS	57	23	+52	40	DW	46	44	+46
GS	52	31	+51	25	AH	40	47	+69
MBs	51	33	+53	37	CE	68	39	+11
WAS	47	33	+52	33	AB	43	42	+11
WT	52	28	+51	31	AR	43	49	+55
					CHH	50	40	—16

TABLE 3—*Hypertension with Myocardial Involvement*

Q Wave Series					Control Series			
Name	Cardio thoracic Ratio (X Ray) per Cent	Cardiac Angle (X Ray) Degrees	Electrical Axis, Degrees	Q Wave (Percentage of Greatest R Deflec tion)	Name	Cardio thoracic Ratio (X Ray) per Cent	Cardiac Angle (X Ray) Degrees	Electrical Axis, Degrees
CO	50	32	+50	62	TTH	45	44	—50
JF	49	31	+55	55	EER	50	38	+73
JRG	55	26	+38	25	LL	50	36	—38
GJ	53	30	+49	76	HB	63	43	—27
Nk	43	28	+46	42	HHF	52	45	+74
CDM	43	27	+55	55	JGH	55	40	+14
FL	48	25	+60	40				
Wb	42	28	+50	46				

TABLE 4—*Miscellaneous*

Q Wave Series					Control Series			
Name	Cardio thoracic Ratio (X Ray) per Cent	Cardiac Angle (X Ray) Degrees	Electrical Axis, Degrees	Q Wave (Percentage of Greatest R Deflec tion)	Name	Cardio thoracic Ratio (X Ray) per Cent	Cardiac Angle (X Ray) Degrees	Electrical Axis, Degrees
HA	57	27	+79	33	ES	45	43	+64
WK	46	35	+68	47	JD	48	45	+72
ON	40	44	+55	40	EJS	52	42	— 9
HL	47	27	+45	62	EM	42	46	+35
JS	53	20	+50	33	MAP	45	40	+86
CES	51	25	+44	50	MS	45	40	+48
FY	50	32	+80	33				
WD	48	33	+47	33				
JE	43	36	+62	44				

TABLE 5—*Normal Heart*

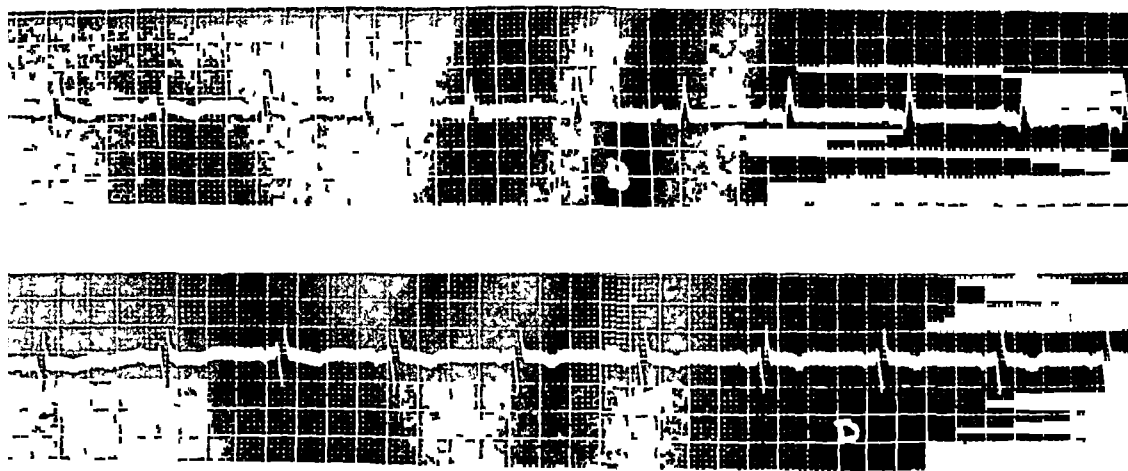
Q Wave Series					Control Series			
Name	Cardio thoracic Ratio (X Ray) per Cent	Cardiac Angle (X Ray) Degrees	Electrical Axis, Degrees	Q Wave (Percentage of Greatest R Deflec tion)	Name	Cardio thoracic Ratio (X Ray) per Cent	Cardiac Angle (X Ray) Degrees	Electrical Axis, Degrees
CA	30	35	+63	33	JKS	42	43	+40
LMB	50	25	+78	50	JMJ	45	42	+54
MB	50	32	+47	37	AWK	45	36	+85
FC	47	30	+44	50	FJK	46	49	+65
TD	46	24	+50	43	WY	44	55	+38
JED	42	25	+41	39	JN	50	38	+58
LJF	50	30	+42	38	HH	43	50	+72
HH	52	31	+42	40	BK	39	46	+71
LJ	45	37	+46	30	WK	41	52	+84
HAK	48	26	+51	30	AN	40	45	+30
GL	45	25	+59	30	JJV	48	41	+40
EL	45	30	+75	45	WJM	43	45	+54
HM	44	31	+46	40	EGP	48	50	+65
EO	50	27	+50	33	RB	41	49	+62
PS	47	27	+62	27	EA	48	40	+50
OS	54	20	+54	50	HES	48	43	+64
ET	45	35	+64	27	TL	44	43	+38
EW	45	33	+55	30	MB	47	40	+47
EJW	47	35	+56	37	ED	40	53	+82
RO	51	25	+54	33	HAM	38	45	+69
					MS	50	45	+43
					CB	48	40	+55
					AAH	45	43	+58

TABLE 6—*Comparison of the Average Angle of Inclination of the Heart in Various Clinical Conditions in the Q Wave Series and in the Control Series*

Clinical Diagnosis	Coronary Disease	Hyper tension	Hyperten sion with Myocardial Involvement	Miscel laneous	Normal Hearts	Average
Q wave series	28 9	30 9	28 4	31 0	29 1	29 6
Control series		43 3	41 0	42 7	44 9	42 9

That the form of the normal electrocardiogram may be influenced by the position of the heart is well known<sup>4</sup> It has been frequently observed that short, stout persons in whom the heart is transversely placed show electrocardiograms indicative of left ventricular preponderance

Cohn<sup>5</sup> has shown that by shifting the location of the leads, or rather by changing the angle of the heart in respect to the leads, from 46 to 6 degrees, a change in the form of the electrocardiogram takes place, and that this form resembles that associated with left ventricular preponderance That changing the position of the heart in a normal person by deep inspiration and deep expiration affects the Q wave also is shown in the accompanying figure It will be seen that on deep inspiration, when the heart tends to assume a vertical



Electrocardiogram showing the effect of change of the position of the heart due to respiration on the Q wave in Lead III A, beginning of deep inspiration, B, holding the breath in deep inspiration, C, beginning of expiration, and D, holding the breath in complete expiration

position, the Q wave is practically absent, while on complete expiration, when the heart is pushed up by the diaphragm and tends to assume a more horizontal position, a large Q wave is present It is also noted that the size of the Q wave increases inversely as the angle of the heart decreases with the change in respiration Pardee<sup>2</sup> has made similar observations in his study He also found that a record taken of

4 Einthoven, W, Fahr, G, and de Wart, A Ueber die Richtung und die manifest Grosse der Potentialschwankungen im menschlichen Herzen und uber den Einfluss der Herzlage auf die Form des Elektrokardiogramms, Arch f d ges Physiol 150 275, 1913

5 Cohn, Alfred E, and Raisbeck, M J An Investigation of the Relation of the Position of the Heart to the Electrocardiogram, Heart 9 311, 1922

a woman during the eighth month of pregnancy shows a large Q wave in lead III, while one taken after delivery shows no Q wave. Pardee stated that a high position of the diaphragm may be a contributory factor in the production of large Q waves in lead III of the electrocardiogram.

Three cases of my series show distinctively the effect of the shifting of the position of the heart due to mechanical causes in the production of Q waves in lead III. In two of the cases ascites was the cause, and in the third marked distention of the abdomen due to gas was responsible for the change of position of the heart.

That there may be other factors involved in the production of the large Q waves is not denied. Purks<sup>6</sup> recently reported his electrocardiographic findings following the ligation of the descending branch of the left coronary artery in man. He noted that the Q wave increased in size after ligation, and exceeded 25 per cent of the greatest R from

TABLE 7—*Association of Negative T Waves with Large Q Waves in Lead III*

T Wave Negativity	Pardee Series		Willius Series		Ziskin Series	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Lead I	1	2.5	28	9.3	7	8.1
Lead I and II	14	9.0	20	6.6	2	2.3
Lead II and III	1	25.0	27	9.0	5	5.8
Lead I, II and III	0	0.0	11	3.7	3	3.4
Total	16	37.2	86	28.6	17	19.6

the fourth to the sixth days, the maximum increase occurring on the fifth day.

A study of the size of the Q waves in the present series shows that the largest Q waves occurred in the cases of coronary disease, 65 per cent of the group showing Q waves larger than 50 per cent of the greatest R. In the group with hypertension together with myocardial involvement, 50 per cent showed a Q wave over 50 per cent of the greatest R, in the group with hypertension alone, 30 per cent showed this characteristic, while in the group with normal hearts 20 per cent showed the Q wave over 50 per cent of the greatest R.

The significance of T wave negativity was compared with the observations of Willius<sup>3</sup> and Pardee,<sup>2</sup> and the results are shown in table 7.

The occurrence of T wave negativity according to leads in my series compares more favorably with that of Willius<sup>3</sup> than that of Pardee.<sup>2</sup> It appears, therefore, that damage to the left ventricle, as a

<sup>6</sup> Purks, W. K. Electrocardiographic Findings Following Ligation of the Descending Branch of the Left Coronary Artery in Man, *Am Heart J* 7:101, 1931.

result of coronary disease, with or without infarction, or of hypertension, may be an associated factor in the production of large Q waves in lead III of the electrocardiogram

#### SUMMARY

In 86 cases in which there were large Q waves in lead III, conforming to the criteria laid down by Pardee,<sup>2</sup> 20, or 23.2 per cent, were found in patients with normal hearts and 33, or 38 per cent, were found in patients with hypertension and with no other sign of cardiac involvement, while 12, or 14 per cent, were found in patients with coronary disease and 8, or 9.3 per cent, in patients with hypertension together with myocardial involvement

A comparison with a control series of an equal number of cases shows that the relative position of the heart within the thoracic cavity is the most common factor associated with the finding of large Q waves. The average angle of inclination of the heart in the group with large Q waves in lead III was 29.6 degrees, while in the control series it was 42.9 degrees, a variation of 13.3 degrees

This variation was constant in all the clinical conditions and also in the normal hearts

The effect of change of position of the heart on the Q wave in lead III as a result of respiration is shown in a record made during inspiration and expiration

The predominance of Q waves over 50 per cent of the greatest R, in the groups with coronary disease and in those with hypertension accompanied by myocardial involvement, the greater distribution of T wave negativity in leads I and II of the electrocardiogram and the experimental evidence introduced showing that ligation of the descending branch of the left coronary artery increases the size of the Q wave in lead III would tend to show that damage to the myocardium of the left ventricle as a result of these conditions is an associated factor in the production of a large Q wave in lead III of the electrocardiogram

# PRODUCTION OF NONFATAL VASCULAR SCLEROSIS IN RABBITS BY MEANS OF VIOSTEROL (IRRADIATED ERGOSTEROL)

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Since the observation that certain substances acquire antirachitic properties following exposure to ultraviolet rays,<sup>1</sup> great interest has centered on the artificial production of vitamin D and on its relationship to the diseases concerned with calcium metabolism. Soon after the initial discoveries, it was established<sup>2</sup> by a series of brilliant investigations that the specific substance activated by irradiation was ergosterol. The efficacy of viosterol (irradiated ergosterol) in the treatment of rickets and osteomalacia was quickly established. In addition, workers<sup>3</sup> studied the effects of this material on normal laboratory animals. They demonstrated that an elevation of the blood calcium occurred and that calcium was deposited in the arterial walls, especially the aorta, and in the muscle of the heart, the wall of the

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From the Pathological Laboratory of the Boston City Hospital

1 Hess, A F. The Antirachitic Activation of Foods and of Cholesterol by Ultra-Violet Irradiation, *J A M A* **84** 1910 (June 20) 1925. Steenbock, H, and Nelson, M T. Fat Soluble Vitamins. XIX. The Induction of Calcifying Properties in a Rickets-Producing Ration by Radiant Energy, *J Biol Chem* **62** 209, 1924.

2 Rosenheim, O, and Webster, T A. The Relation of Cholesterol to Vitamin D, *J Biol Chem* **21** 127, 1927. Heilbron, I M, Kamm, E D, and Morton, R A. The Absorption Spectrum of Cholesterol and its Biological Significance with Reference to Vitamin D, *ibid* **21** 78, 1927, *Nature* **120** 617, 1928. Pohl, R. The Absorption Spectrum of the Antirachitic Vitamin, *Nachr v d Gesellsch d Wissensch zu Gottingen, math-physik Kl*, 1926, p 185. Windaus, A, and Hess, A. Sterol and Antirachitic Vitamin, *ibid*, 1926, p 175. Bills, C E, Honeywell, E M, and MacNair, W A. Antiricketic Substances. Biochemical and Spectroscopic Studies on Purified Cholesterol, *J Biol Chem* **76** 251, 1928.

3 Pfannenstiel, W. A Summary of Recent Work on Vigantol (Irradiated Ergosterol), *Lancet* **2** 845 (Oct 20) 1928. Kreitmair, H, and Moll, T. Hypervitaminosis Through Large Doses of Vitamin D, *Munchen med Wchnschr* **75** 637, 1928. Klein, I J. Effects of Massive Doses of Irradiated Ergosterol, *J A M A* **92** 621 (Feb 23) 1929. Smith, M I, and Elvove, E. The Action of Irradiated Ergosterol in the Rabbit, *Pub Health Rep* **44** 1245, 1929. Shohl, A T, Goldblatt, H, and Brown, H B. Pathological Effects upon Rats of Excess Ergosterol, *J Clin Investigation* **8** 505, 1920.



stomach, the lungs and the kidneys. In still other experiments<sup>4</sup> it was shown that even more widespread calcification occurred, and that the animals frequently had a retention of nitrogenous products in their blood before death.

There has been fairly general agreement that the deforming, sclerotic changes of the aorta were most extensive in the ascending and transverse portions, and that the bronchial cartilages and kidneys contained marked deposits of calcium. In general, the previous workers confined their observations to the study of the terminal changes in the tissues, after the animals died from poisoning with viosterol. However, some attempted, by killing the animals during the course of medication, to demonstrate the progression of the lesions. Schiff<sup>5</sup> observed a period of partial recovery in some of her animals between the administration of the last dose of viosterol and the subsequent spontaneous death.

In view of the specific manner in which viosterol produces severe lesions in the organs of such great clinical importance as the aorta, lungs and kidneys, it seemed of especial importance to damage extensively these structures without causing the death of the animal.

The present paper deals with the production of such lesions in rabbits, without causing their death. Also the residual changes after the animals were killed (three and one-third months later) were studied.

#### MATERIALS AND METHODS

The four young rabbits used averaged 1,600 Gm in weight and were fed on the usual laboratory diet. A preparation of viosterol, "10,000 D,"<sup>6</sup> having ten thousand times the antirachitic potency of cod liver oil was administered by stomach tube, in individual doses of from 5 to 7 cc at intervals of from four to five days. At times the animals were freed from medication for one or two weeks ("rests," while recovering from toxic doses). The total duration of the period of administration (including "rests") ranged from forty to seventy days. The animals were then allowed to recover and later were killed, from ninety-seven to one hundred and two days after the final dose of viosterol was given. Determinations of the blood urea were made at the beginning of the experiment and about one week after the cessation of medication.

A series of three control animals received the nonactive solvent oil that was used in the preparation of the viosterol employed.

Soon after the gross examination of the organs, sections were fixed in an alcohol-formaldehyde mixture (9 parts of 95 per cent alcohol to 1 part of 40 per cent formaldehyde), in 10 per cent formaldehyde, in 95 per cent alcohol and in

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4 Spies, T. D. The Calcification of Tubercles by Means of Irradiated Ergosterol, *Am J Path* 6:337, 1930. Spies, T. D., and Glover, E. C. Renal Lesions with Retention of Nitrogenous Products Produced by Massive Doses of Irradiated Ergosterol, *ibid* 6:485, 1930.

5 Schiff, A. Changes Produced in Blood Vessels by Vigantol, *Virchows Arch f path Anat* 278:62, 1930.

6 This preparation was furnished through the courtesy of Mead Johnson & Company.

**Zenker's fluid** Some of the tissues fixed in formaldehyde were embedded in celloidin and stained with either hematoxylin and eosin or by the silver method of von Kossa. The tissues fixed in Zenker's fluid were embedded in paraffin and stained with eosin-methylene blue (methylthionine chloride, U S P) and in some instances with Weigert's elastic tissue stain. The deposits of calcium were identified by their solubility in acid and by the following histologic criteria, using principally formaldehyde-fixed material: (1) When stained with hematoxylin and eosin, the precipitated calcium appeared as a dark blue, coarsely granular material, (2) after treatment with silver nitrate solution and counter-staining with a 0.5 per cent solution of basic fuchsin, the deposits assumed a deep brownish-black color.

#### OBSERVATIONS

A temporary loss of the rabbit's body weight occurred soon after the administration of viosterol was begun. Cachexia, loss of appetite and sometimes diarrhea developed as the administration was continued. Several times the animals appeared so near death that the administration of the substance was discontinued for from seven to fourteen days. Soon after receiving the final dose of viosterol the animals began to eat better and gain weight, and they still had normal readings for blood urea. A few weeks later they appeared in splendid health and continued to gain weight until they were killed.

The control animals gained weight and appeared healthy throughout the experiment.

#### PATHOLOGIC DESCRIPTIONS

While the organs of all animals were examined grossly and microscopically, only the changes in the aorta, lungs and kidneys will be described in this report.

**Aortas**—The aortas from the four animals that received viosterol appeared as thick-walled, rigid tubes. The sclerotic process extended from the aortic cusps to the iliac bifurcation. However, the ascending aorta and the transverse arch were especially involved. Here the vessels showed aneurysmal dilatation (often twice the diameter of normal). They were hard (calcified),<sup>f</sup> irregular in contour and tortuous. The remaining portion of the aortas was affected in the same manner, but to a progressively less degree as the examination approached the iliac bifurcation. It was obvious from the external appearance that the deformity of the walls was caused by innumerable areas of varying sizes and shapes in the walls, which often bulged out from the lumina. In a few instances the lesions protruded inward so as to reduce the caliber of the vessels. The intimal surface was occupied by the same type of closely situated deforming areas. They ranged from 0.6 to 0.2 cm. across, and their contiguous borders were separated by thin partitions, which were usually seen to lie transversely to the axis of the aorta. The lining was smooth, free from ulcerations and firm. When

a cross-section of the aorta was taken, the media was found to contain a grayish-white material (calcium)

The aortas of the control animals were normal

*Lungs*—The lungs from the animals receiving viosterol were of normal size, shape and color. The trachea and larger bronchi were thickened and abnormally rigid. They were free from exudate. When these were sectioned, a grayish-white line could often be seen within their walls. The parenchyma and pulmonary vessels appeared normal.

The lungs from the control animals were normal.

*Kidneys*—The kidneys from the animals that received viosterol were normal in size, shape and consistence. However, after sectioning, innumerable small, but easily visible, grayish-brown lesions (calcium) could be seen throughout the cortex. Similar deposits were grouped in the medulla to form a thin strip which ran parallel to the curve of the cortex, 0.2 cm medial to its inner border. In all instances the cortex and medulla were well demarcated and of normal thickness.

The capsule of each kidney was thin, it stripped with ease and left a smooth, glistening surface. Mild sclerosis was observed in a few of the large branches of the renal arteries. The pelvis appeared normal.

The kidneys from the three control animals were normal.

#### MICROSCOPIC DESCRIPTION (FORMALDEHYDE FIXATION)

*Aortas*—The aortas from all animals that had received viosterol were severely deformed. Many irregularly sized and shaped areas of hyalinization and calcification were distributed through the media. The medial changes were usually most marked in the region of the internal elastic lamina. Almost the entire wall was involved in the more advanced lesions, but in the less involved regions the change was limited to small portions of the internal elastic lamina and sometimes to the adjacent portions of the media. In the latter areas, the adjacent hyalinized and calcified foci had not fused to form an encircling layer around the lumen. Oftentimes the adjacent edges of these lesions were separated by normal-appearing tissue. The elastic tissue was usually severely damaged. At times the fibers appeared hyalinized, but in other instances they were irregular in size, shape and distribution. In the still more advanced lesions, the elastic tissue could not be identified.

It is noteworthy that the aortas in this series were slightly less involved than those previously studied.<sup>4</sup> It is worthy of emphasis that the larger lesions in the aortas of the present series contained more necrotic cellular debris and less visible calcium than comparable lesions from the aortas of the animals studied previously. It seemed as though

the lesions of the present series of animals had a relative increase in the degenerative process and a relative lack of the extensive deposits of calcium. Does this mean that the affected cells go on to degeneration and that some of the deposited calcium has been reabsorbed by the animals?

The aortas from all control animals were normal.

*Lungs*—The trachea and bronchial cartilages taken from the animals that had received viosterol were heavily calcified. In many instances the area of calcium deposition within the trachea was as large as 0.1 cm. A thin concentric area of hyalinization and calcification was situated just beneath the bronchial epithelium. The tracheal

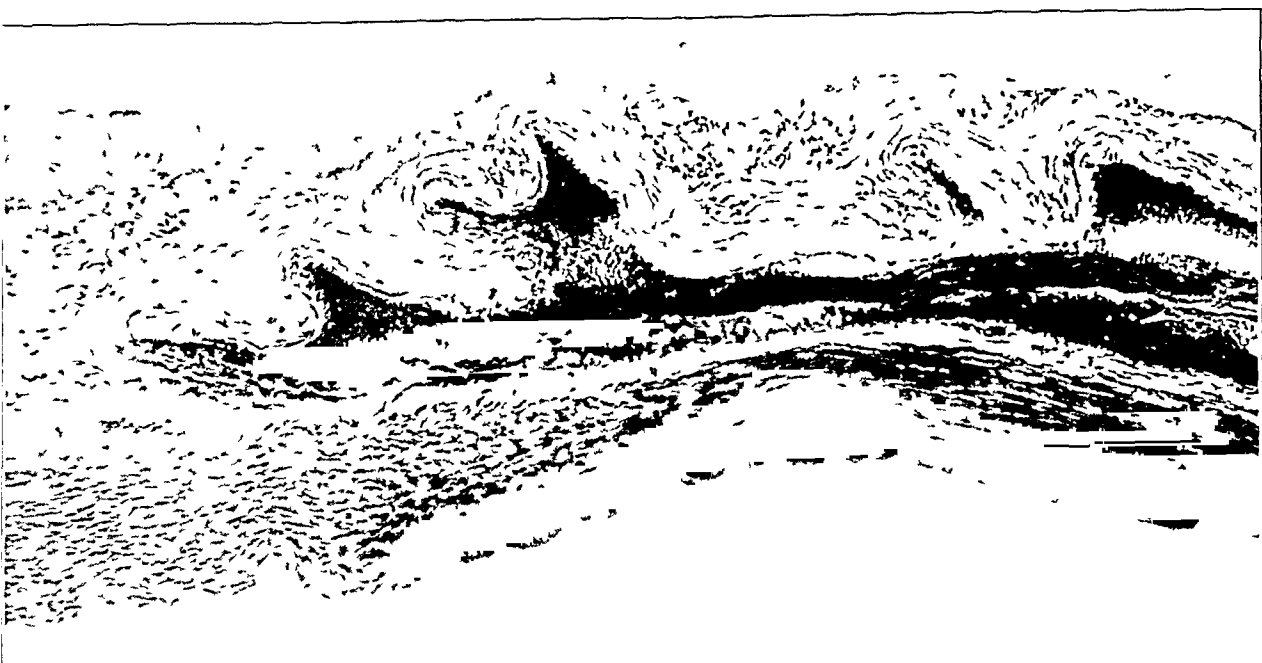


Fig 1—Photomicrograph of a slightly involved area of the aorta. Note the deposit of hyaline material and calcium in a layer. The adjacent tissue appears normal,  $\times 117$ .

and bronchial epithelium was frequently calcified, and at times the alveolar epithelium contained deposits of calcium. Calcification was absent within the walls of the vessels.

The trachea and lungs of the control animals were normal.

*Kidneys*—The kidneys from all animals that had received viosterol were conspicuously involved. The arteries, arteriole, tubules and glomerular capsules were prominently hyalinized and calcified. In general, these lesions were similar to, but less extensive than, the lesions previously described<sup>4</sup>. It is interesting that the renal lesions in the animals of the present experiment contain less visible deposited calcium than comparable lesions in the renal tissues described in the former experiments. On the other hand, the hyalinization process appeared more prominent in some of the comparable lesions of the

present series than in the former experiments. The hyaline calcification were so intimately related that the reactivity of of calcium would cause an apparent increase in the amount of formation. It is also noteworthy that the deposits of calcium strikingly fewer in the tubules of the kidneys of this series. The apparent decrease in the prominence of the deposits of calcium near that the calcium has in part been excised.



Fig 2—Photomicrograph of a severely involved area of the aorta. Note the splitting of the wall and the presence of hyalinized material and calcium, reduced from a magnification of  $\times 117$ .

#### ZENKER'S FIXATION

Calcification was absent in all tissues fixed in Zenker's fluid because the acetic acid had removed the precipitated calcium from the tissues. Hyalinization of the involved sites was extensive. The sites of calcification in the aorta, lungs and kidneys now appeared as poorly stained, faintly blue areas. These areas were hyalinized, and in many instances cellular detail was obscured, but in others vacuolated cells and pyknotic nuclei were observed. In some regions polymorphonuclear and endothelial leukocytes were found in the fused masses of necrotic material.

## COMMENT

the results shown in the experiments reported here that the administration of repeated, massive doses of viosterol produced a severe and extensive sclerosis of the aorta and renal vessels. This phenomenon was associated with calcium deposition within the parenchyma of the lung and kidneys. It is worthy of emphasis that soon after the final dose of 105 mg. all animals regained their appetites and body weight. They continued to have normal renal function. At the termination of the experiment, they appeared in the best of health.

In general, the vascular process was one of extensive sclerosis with hyalinization and calcification of the media. The pulmonary changes consisted of calcification of the trachea, bronchial cartilages and, at times, bronchial and alveolar epithelium. Deposits of calcium were absent in the pulmonary vessels. The renal arteries, arterioles, tubules and glomerular capsules were hyalinized and calcified.

The lesions in this series of experimental animals were slightly less prominent than the lesions of the animals that were allowed to die from poisoning with viosterol. However, they are considerably more extensive than the lesions produced by some other workers who allowed the animals to die from massive doses of viosterol. The lesions studied, three and a third months after their production, were extreme, and I think that they represent about the maximal degree of involvement compatible with the animal's return to apparent health.

In many lesions of the present series of experimental animals the apparent proportion of hyalinized tissue to microscopically visible calcium was greater than in comparable lesions of the previous experiments, thus suggesting that some of the calcium had been reabsorbed during the three or four months after cessation of medication. Naturally, the vascular deformity would be expected to remain despite any tendency of calcium reabsorption. The vascular sclerosis produced in these experiments is not the result of spontaneous atherosclerosis, which sometimes occurs in older rabbits. Also, the experimental lesions do not in any way resemble the changes found in the aortas of rabbits following the administration of cholesterol or unirradiated ergosterol. It seems that this study gives a method of producing permanent severe sclerosis of the aorta and renal vessels.

## SUMMARY AND CONCLUSIONS

1 It has been shown in the experiments reported here that severe and persistent damage can be produced in such vital organs as the aorta, lungs and kidneys without causing death to the animals by repeated administration of toxic doses of viosterol.

2 A comparative study of the residual lesions in this experiment with similar lesions in previous work suggests that the animal was in time able to reabsorb some of the deposited calcium.

TRANSIENT VENTRICULAR FIBRILLATION  
THE CLINICAL AND ELECTROCARDIOGRAPHIC MANIFESTATIONS  
THE SYNCOPAL SEIZURES IN A PATIENT WITH  
AURICULOVENTRICULAR DISSOCIATION

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In a recent communication<sup>1</sup> it was pointed out that periods of unconsciousness in patients with auriculoventricular dissociation are associated with transient seizures of ventricular fibrillation much more commonly than has been suspected hitherto. Attention was called to the fact that a clinical diagnosis of transient ventricular fibrillation may be suspected in such patients if preceding a period of unconsciousness the heart rate has been noted to increase above that of the usual basic rate.

Within the past few months we have been able to confirm these findings in another woman with complete auriculoventricular dissociation and transient syncopal seizures in whom some of the premonitory periods preceding the attacks of unconsciousness resembled those observed in our previous case. However, on careful study of the electrocardiograms obtained at the same time that the patient was observed clinically, another type of cardiac mechanism was found to precede the periods of unconsciousness.

In view of the fact that the alterations in rhythm lend themselves to a clinical analysis, it becomes increasingly important to appreciate them, since hitherto little attention has been paid to the various mechanisms responsible for syncopal seizures in patients with heart block.

REPORT OF CASE

*History*—M. G., a Jewish woman, aged 65, was admitted to the Montefiore Hospital on Sept. 9, 1931. Her chief complaints on admission were recurrent seizures of unconsciousness accompanied at times by convulsions and attacks of precordial pain. These symptoms were of six months' duration.

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1. Schwartz, S. P. Transient Ventricular Fibrillation. A Study of the Electrocardiograms Obtained from a Patient with Auriculoventricular Dissociation and Recurrent Syncopal Attack, *Arch. Int. Med.* 49:282 (Feb.) 1932.

the patient was ill and up and about until October, 1930, when she had the first time of precordial pains, which usually came on at night. They were sharp, localized to the midsternal area. They bore no relationship to meals and exertion. The cause of the accompanying symptoms of sweating and "pallor" she was unable to determine.

The patient began to suffer from periodic attacks of unconsciousness of 10 to 15 minutes at a time and associated with incontinence of both urine and feces. One of her family who saw her in these attacks described them as follows: The patient suddenly without any warning. The patient had been seen to become very pale and then intensely blue and had convulsions of all extremities would end. During such episodes the patient would awaken and scream loudly, not knowing what had happened to her in the previous few minutes.

Occasionally the convulsive seizures were followed by a semicomatose period lasting as long as five hours, with the patient only gradually regaining orientation. During such times her speech would be unintelligible.

In June, 1931 she entered the Lebanon Hospital, where it was noted that her pulse rate was slow, averaging between 28 and 38 beats per minute. The recurring attacks of unconsciousness were diagnosed as Stokes-Adams seizures in a patient with a slow heart rate. On the assumption that they were due to standstill of the ventricles, the patient was given barium chloride in doses of 30 mg three times a day and epinephrine hydrochloride in doses of 0.5 cc of the 1:1,000 solution sometimes three and sometimes four times a day intramuscularly.

Instead of improving under this form of therapy, she became worse. Indeed, in reviewing the number of syncopal seizures during her stay at the Lebanon Hospital, it was almost impossible to believe that she had had so many attacks in a single day. Therapy was continued until the day of her transfer to our institution.

*Physical Examination*—Examination on admission to the Montefiore Hospital revealed an old woman lying comfortably in bed with only one pillow under her head. Her face had a peculiar yellow, grayish color. The superficial veins of the neck were moderately distended, but they did not show any auricular pulsations. The right carotid artery was thick and tortuous. The apical impulse of the heart was in the sixth intercostal space in the anterior axillary line. The heart sounds were of poor quality. They varied in intensity from beat to beat. The heart rate was between 32 and 50 beats per minute, it was irregular, with only about two thirds of the heart beats causing a pulse in the radial artery.

The blood pressure was 170 mm of mercury systolic and 60 mm of mercury diastolic.

The lungs showed moderate moisture at both bases posteriorly. The abdomen was lax and soft, and the edge of the liver was barely palpable. The lower extremities showed slight pitting edema.

Roentgen examination of the chest revealed moderate pulmonary congestion and marked dilatation of the cephalobrachial vessels.

The heart was placed horizontally and showed moderate general enlargement of the left ventricle. The arch of the aorta was elongated and dilated, and there were numerous calcific areas in it.



An electrocardiogram made on the day following admission showed complete auriculoventricular dissociation with a regular ventricular rate of 23 and a regular auricular rate of 66 beats per minute. The ventricular complexes were all of the upright form, they were supraventricular in type, and they varied in size from beat to beat.

The Wassermann reaction of the blood was negative.

The unusual history that this patient presented prompted us to place her, immediately after admission, under close supervision, and for the four months following her admission to the Montefiore Hospital she was seen and studied preceding, during, and subsequent to several hundred attacks of unconsciousness. More than a hundred of these attacks were recorded electrocardiographically, and they all proved to be due to ventricular fibrillation. From the clinical correlations of these records we have been able to appreciate the variations in the heart rate and rhythm preceding and succeeding ventricular fibrillation.

#### THE NATURAL COURSE OF TRANSIENT VENTRICULAR FIBRILLATION

The natural course of the syncopal attacks due to transient ventricular fibrillation in the patient is unusual. The seizures were variable from day to day, and on the same day they varied from hour to hour. They showed no definite diurnal or nocturnal periodicity. They occurred as frequently during the patient's deep sleep as when she was awake. They had no relationship to meals, exertion or defecation. It was impossible to produce them by exercise. However, fright and emotional disturbances seemed to induce their appearance.

During the four months she has been under observation, she has not passed a single day without having at least one syncopal attack due to ventricular fibrillation. She has been seen in as many as two hundred and seven attacks of unconsciousness during a period of twenty-four hours, at the end of which time she did not present any physical findings different from those seen on the previous day when she had only a few minor seizures (table).

The attacks varied in duration from only a few seconds each to close to six minutes. The longer seizures were invariably accompanied by incontinence of either feces or urine. The average duration of these seizures was approximately forty-six seconds.

The shorter attacks did not influence the sensorium. The longer attacks, usually those lasting a few minutes at a time and coming in frequent succession, clouded the memory. Following such an experience the patient would speak unintelligently for several hours at a time, and frequently she would go into a semistuporous condition from which she could be easily aroused.

She did not complain of any precordial distress. Occasionally she was nauseated and frequently vomited during a seizure without her knowledge, for she was unconscious.

Only at one time did we note any tenderness over the hepatic region following a long series of these seizures, and on several occasions pitting edema of the legs was present. Even now her lungs are remarkably free from moisture.

In the periods preceding the attacks, the patient was not aware of any peculiar precordial sensations, nor did she experience any palpitations of the heart.

*Number of Syncopal Attacks Due to Ventricular Fibrillation Experienced by the Patient During a Period of Twenty-Four Hours, at a Time When the Attacks Were Unusually Frequent*

Date and Time of Day	Duration, Seconds	Date and Time of Day	Duration, Seconds	Date and Time of Day	Duration, Seconds	Date and Time of Day	Duration, Seconds
10-30-31 p m		10-30-31 p m		10-30-31 p m		10-31-31 a m	
1 00	20	4 25	10	7 55	1	3 30	1
1 32	30	4 28	20	7 56	1	3 50	2
1 35	40	4 31	25	7 59	1	3 51	1
1 40	20	4 34	30	8 00	15	4 00	18
1 41	5	4 35	7	8 05	7	4 05	1
1 44	15	4 41	20	8 10	62	4 10	2
1 47	20	4 43	60	8 15	22	4 15	18
1 48	20	4 46	20	8 16	34	4 20	15
1 49	8	4 50	25	8 20	38	4 25	2
1 51	2	4 55	10	8 25	1	4 35	16
1 55	25	5 02	20	8 29	32	5 00	10
1 59	5	5 04	30	8 30	1	5 03	18
2 00	28	5 07	25	8 31	26	5 20	10
2 10	10	5 14	15	8 37	4	5 30	11
2 12	30	5 15	130	8 45	31	5 44	17
2 17	30	5 22	35	8 48	3	6 00	8
2 19	10	5 25	30	8 55	2	6 10	10
2 21	8	5 31	3	9 00	70	6 15	2
2 25	15	5 40	25	9 02	1	6 35	17
2 27	25	5 43	5	9 10	12	6 37	15
2 31	3	5 45	4	9 15	18	6 50	24
2 33	30	5 58	10	9 22	2	6 56	20
2 35	8	5 59	30	9 25	30	7 10	20
2 41	23	6 00	4	9 30	13	7 15	40
2 44	4	6 30	2	9 35	20	7 20	5
2 47	2	6 31	10	9 37	20	7 30	25
2 58	3	6 32	2	9 40	22	7 45	6
2 59	1	6 38	2	9 41	23	8 00	5
3 01	40	6 46	10	9 43	15	8 15	3
3 15	15	6 50	20	9 45	20	9 00	10
3 16	1	6 52	40	9 49	2	10 05	2
3 18	4	6 56	2	9 50	12	11 04	90
3 21	35	6 58	40	9 51	8	11 25	35
3 26	2	7 07	2	9 54	7	11 27	62
3 29	20	7 11	10	10 00	3	11 32	24
3 31	5	7 13	40	10 05	1	11 55	15
3 34	3	7 20	3	10 35	2	p m	
3 36	2	7 22	1	11 00	2	12 45	45
3 40	50	7 25	3	11 45	2	12 55	24
3 46	40	7 30	2	10-31-31		12 57	8
3 58	35	7 35	1	a m		1 07	20
4 00	35	7 37	1	12 10	1		
4 05	10	7 39	1	12 30	1		
4 09	35	7 40	1	1 50	2		
4 10	15	7 41	1	2 30	14		
4 16	4	7 45	6	2 31	2		
4 17	20	7 46	4	2 46	16		
4 20	10	7 48	1	3 00	21		
4 21	30	7 50	3	3 20	10		
4 24	25	7 51	1	3 25	27		

THE CLINICAL MANIFESTATIONS PRECEDING TRANSIENT SEIZURES  
OF VENTRICULAR FIBRILLATION

The stages preceding a period of transient ventricular fibrillation were extremely uniform as compared with those reported previously.<sup>1</sup> Obviously the premonitory periods with their changes in rhythm varied in duration preceding each attack, but their mode of onset was practically the same.

The basic ventricular rate preceding an attack averaged 28 beats per minute and was only slightly irregular (fig 1 *A* and *B*),<sup>2</sup> but this irregularity could not be appreciated clinically. The auricular rate was 66 beats per minute. The auricular contractions could not be heard during the interventricular silences. However, on listening to the apical region at such times a definite change in the quality of the heart sounds

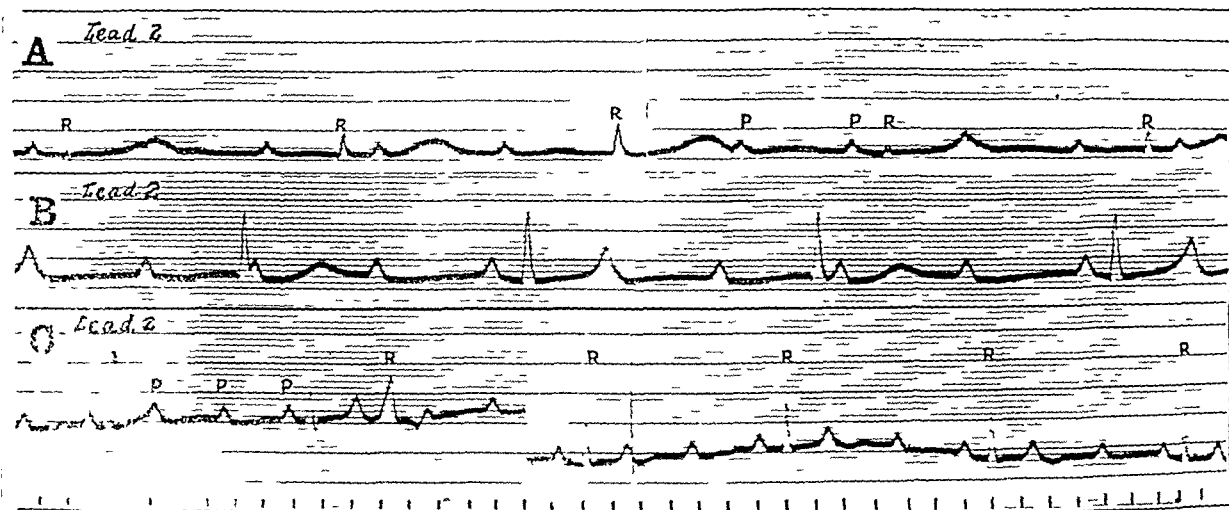


Fig 1—*A*, complete auriculoventricular dissociation. The basic ventricular rate is 28 beats per minute. The voltage of both the auricular and the ventricular complex is low. There is a variability in the size, shape and form of the main ventricular complexes from beat to beat. The auricular rate is 66 beats per minute. *B*, compare the voltage of the auricular and ventricular complexes with those in *A*. At such times the heart sounds were louder. *C*, partial heart block. The auricular rate is 120, the ventricular rate is 40.

could be made out. For a period of several minutes they could be heard distinctly and clearly, and then there would be a sudden transition to lower pitched and weaker sounds that were barely audible. At the same time the quality of the pulse also changed, suddenly becoming weaker and remaining so until the heart sounds increased in intensity again.

During the presence of the weak heart sounds, the electrocardiograms revealed low voltage of both the auricular and the ventricular

<sup>2</sup> All of these studies were carried out with lead 2 only.

complex (fig 1 *A*), whereas when the heart sounds were more audible, the voltages of these complexes were higher (fig 1 *B*)

Occasionally the basic ventricular rate would increase suddenly from an average of 28 beats per minute to 40 beats. At such times the electrocardiogram invariably revealed partial heart block with a 3 to 1 rhythm, a ventricular rate of 40 and an auricular rate of 120 beats (fig 1 *C*)<sup>3</sup>. Syncopal seizures were not observed to follow any of these transitions from partial to complete heart block or vice versa, although we have obtained records of transient ventricular fibrillation during the presence of already established partial heart block. Frequently during the presence of both these regular rhythms, the Q-R-S complexes were variable from beat to beat in height as well as in duration, often assuming transitional changes from a dextrocardiogram to a levocardigram and back again.

The ventricular rates during the presence of both partial and complete heart block were not influenced by exercise or sleep.

After several hours at one time and only several minutes at another, when the patient was feeling perfectly well, her ventricular rate, which averaged 30 beats per minute, would be suddenly disrupted by the appearance of alternate premature ventricular beats (fig 2 *A*, *B* and *C*) which could be heard at the apex and distinctly felt at the pulse. Sometimes these premature beats would come in groups of 2 or more, all of them appearing to arise from different foci in the ventricles (fig 2 *B*).

It was soon noted, however, at such times, when observations were made of the movements of the galvanometer string at the same time that the heart sounds and pulses were studied clinically, that when these extraventricular oscillations increased in frequency (fig 2 *E* and fig 3 *A*, *B* and *C*) only the first 4 beats following a basic ventricular complex could be heard at the apical region of the heart. These became progressively weaker in quality from beat to beat, so that all the oscillations appearing after the fifth one could be registered electrocardiographically, but could not be heard at the apical region of the heart.

With a little practice it was possible to learn these events in their order of sequence clinically so that we could predict the increase in the frequency of the ventricular oscillations and their duration by the appearance of "silent" pauses that interrupted the rhythm of the heart. As these pauses increased in number, the patient began to complain of dizziness, and she would shut her eyes momentarily.

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3 This type of rhythm during the presence of complete auriculoventricular dissociation may be due to a fortuitous adaptation of the auricles to the ventricles. In this patient, however, the ventricles could be slowed at first by epinephrine at such times, indicating that the auriculoventricular pacemaker was under the influence of the vagus, consequently, the block was "partial."

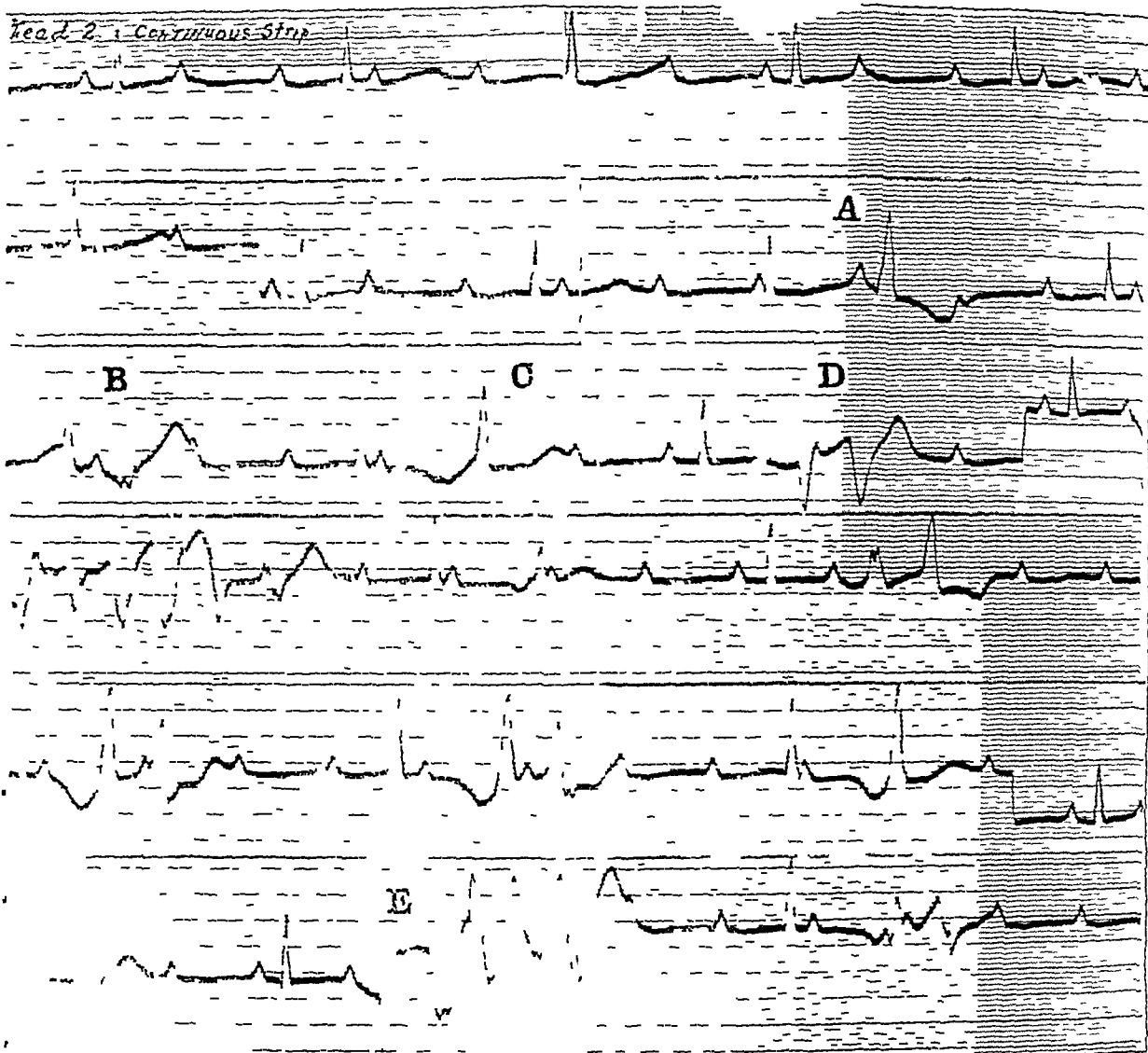


Fig 2—The premonitory period. Complete auriculoventricular dissociation. The basic ventricular rhythm interrupted by the appearance of alternate premature ventricular beats (A, B, C), which are sometimes upright, but more usually are downward (D, E).

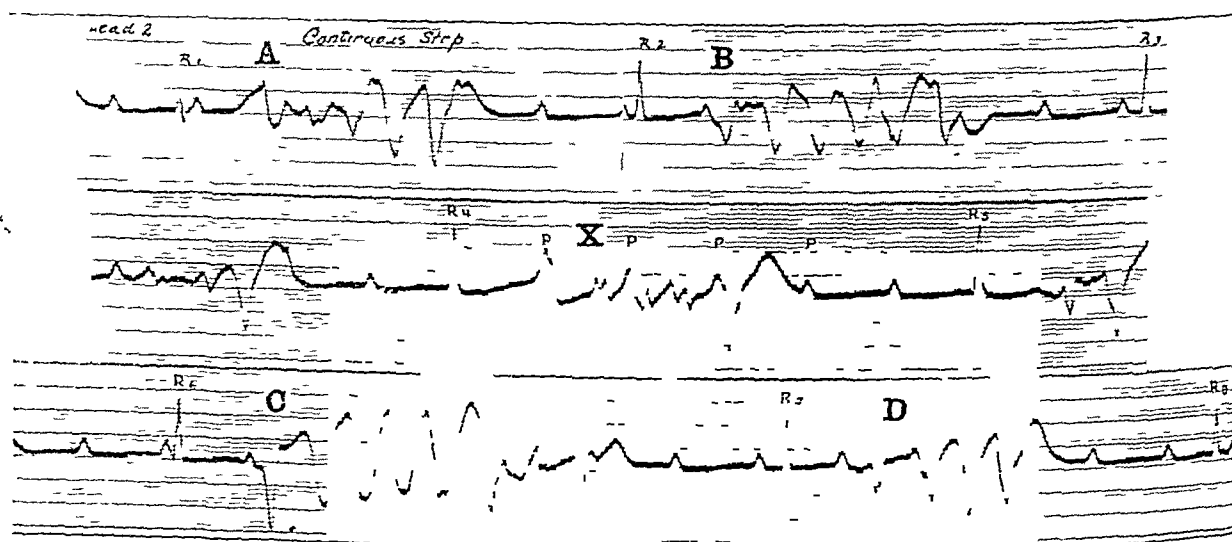


Fig 3—The premonitory period. Recurrent groups of aberrant ventricular oscillations interrupting the basic rhythm. At such times the patient showed alternate pallor and redness of the face. The auricular sequence is not disturbed (X).

With further practice it no longer became necessary to resort to auscultation of the heart to determine such pauses, because when the fingers became accustomed to the variations in the radial pulsations we could tell the presence of the ventricular oscillations. For, after a strong pulse a pause was found to follow successively several progressive shorter and weaker pulse beats. While clinically to the casual observer this premonitory period would appear as a reduction in the ventricular rate, actually there was a definite increase in it if we are to include the few heart sounds and palpable pulsations at the wrist that follow each basic ventricular complex, so that a heart rate of 30 beats would be increased rapidly to one of 50 when single premature beats appeared and to one of a higher rate when more appeared in rapid succession.

Sometimes the ventricular oscillations following the basic ventricular complexes appeared in recurrent groups (fig 3 *A, B, C* and *D*), resulting in a disappearance of the pulse of from five to six seconds. After a while it was possible to associate this mechanism with an alternate pallor and flushing of the face, the pallor resulting from ineffectual peripheral circulation during the presence of the ventricular oscillations and the redness coming on with the marked forceful contraction of the ventricles associated electrocardiographically with the basic ventricular complex.

When the basic ventricular rhythm was interrupted by periods of ventricular fibrillation for a period longer than eight seconds, but for not more than twelve seconds, the patient's face assumed a deathly pallor, she shut her eyes and lapsed into momentary unconsciousness, to be suddenly awakened and startled as her face assumed a ruddy complexion, which coincided with a forceful beat of the heart.

Such short periods of unconsciousness of from eight to twelve seconds would invariably predicate and herald a typical major attack of syncope. Even during these shorter syncopal accidents (fig 4 *A* and fig 5 *A* and *B*) the patient was incontinent of feces and of urine.

#### THE ALTERATIONS IN THE ELECTROCARDIOGRAM PRECEDING TRANSIENT VENTRICULAR FIBRILLATION

The initial ventricular complexes of the recurring groups of ventricular oscillations that begin to disrupt the basic rhythm so as to increase the ventricular rate and indicate the approach of a syncopal seizure are extremely variable, as may be gained from the accompanying records.

Sometimes (comparisons are made of lead 2 only) these complexes are aberrant and of the upright form, with unusually large T waves (fig 2 *A*). Occasionally they are extremely bizarre, of low voltage and

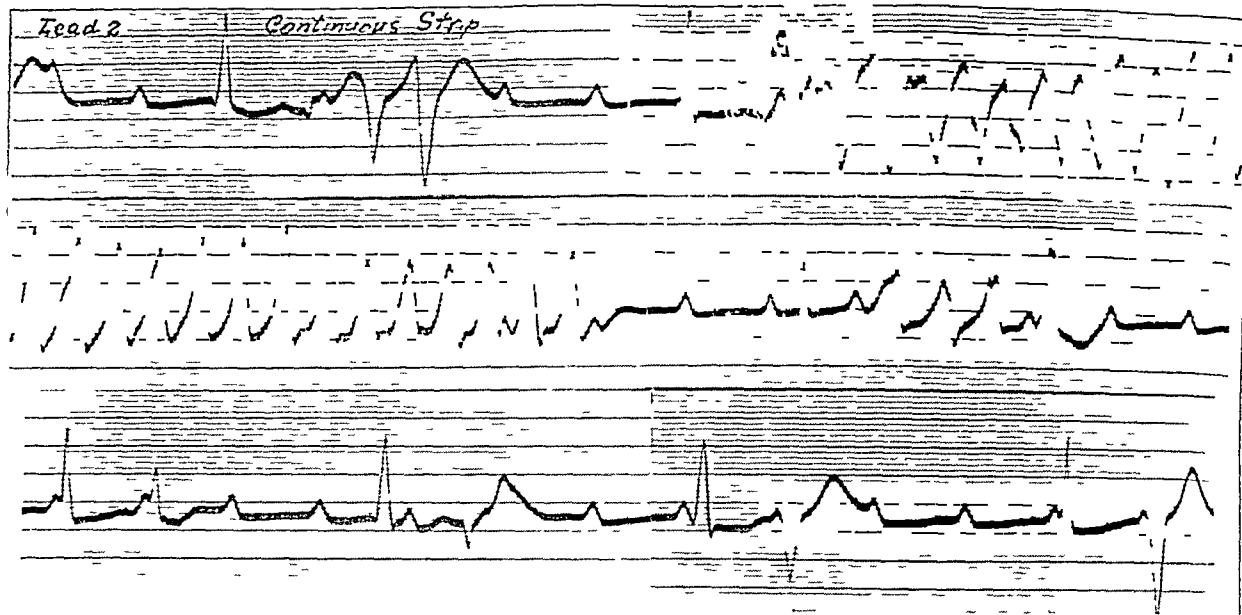


Fig 4—The premonitory period The basic ventricular rhythm is interrupted by a series of aberrant ventricular oscillations (A), only the first four of which could be heard at the apex of the heart or felt at the radial pulse During such periods of approximately eight seconds' duration, the patient's face was pale and her eyes were shut

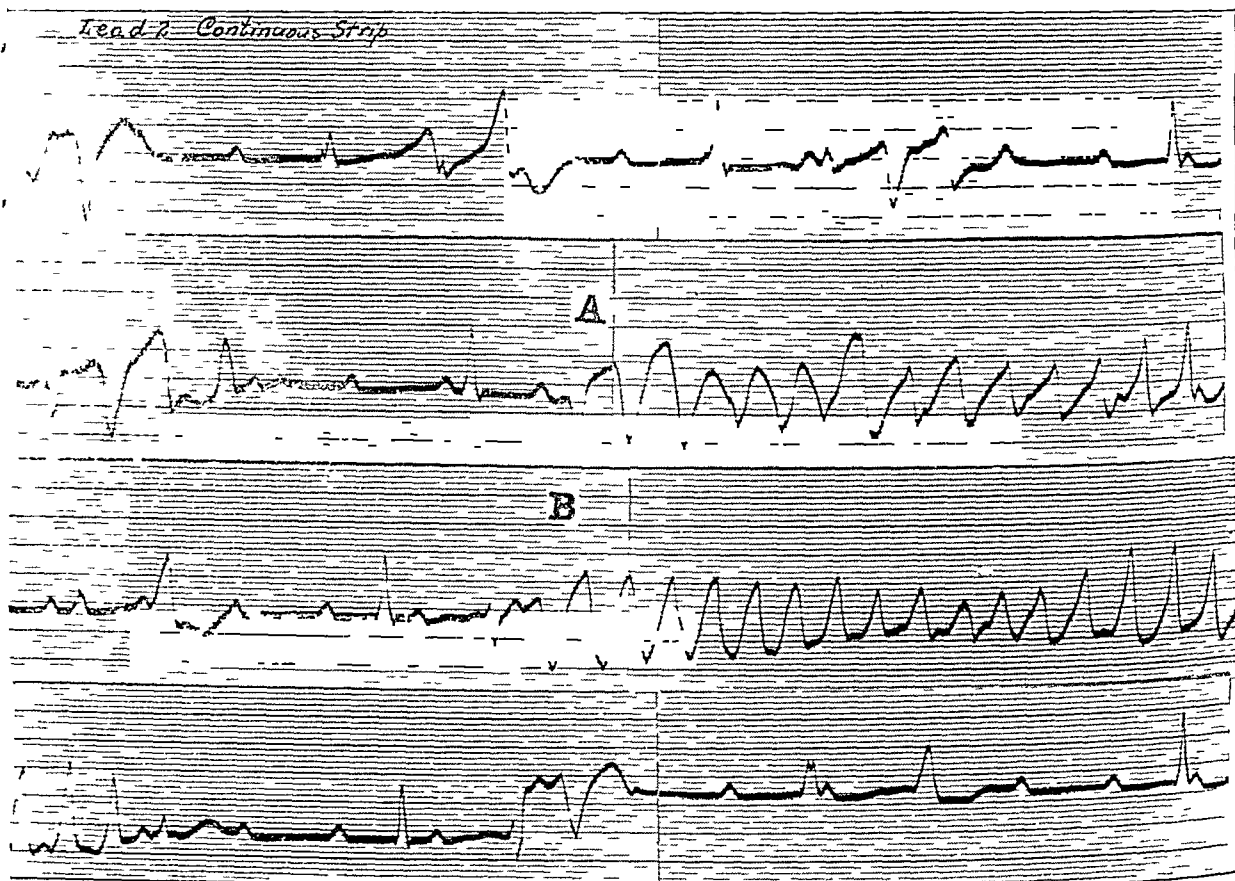


Fig 5—The premonitory period Recurrent groups of aberrant ventricular oscillations of about five seconds' duration associated with a disappearance of the heart sounds and the pulse during their presence Note that the ventricular deflection initiating these periods (A, B) is downward as a rule

very wide (fig 3 *A* and *B*). Most frequently, however, the initial deflection consists of an extrasystole that is practically always of the same shape and almost of the same size and form (fig 2 *D*, fig 3 *C*, fig 4 *A* and fig 5 *A*).

The electrical complexes that follow the initial ventricular beat are wide (0.32 second), aberrant deflections that resemble those seen in patients with disturbed conductivity in the bundle branches when the voltage is as high as 20 mm (fig 2 *E*, fig 3 *C* and *D* and fig 5 *A* and *B*) or approach closely records that resemble arborization block (fig 6 *B*). Beat by beat they sometimes decrease in size as the frequency of the oscillations is increased, and at times they increase in size (fig 3 *A* and *D*) for a few beats until they reach a standard size and sometimes remain so with but slight fluctuations throughout a seizure of syncope.

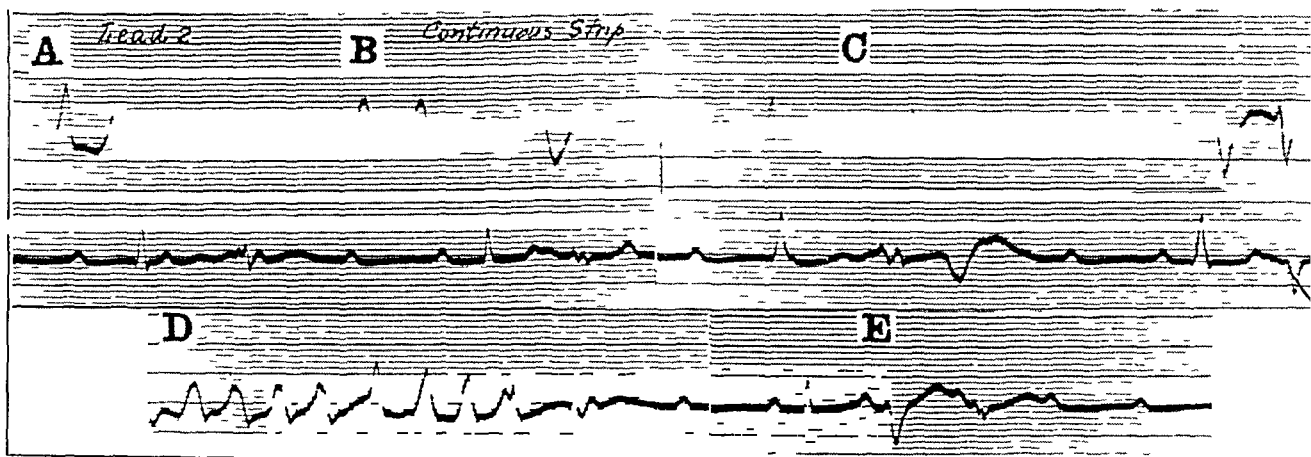


Fig 6—The premonitory period. When the voltage of the ventricular complexes of the basic rhythm is low, then the voltage of the aberrant ventricular oscillations appearing at such times is low. Compare 6*B*, *C* and *D* with 5*A* and *B* of the previous record.

The sequence of the auricular beats is not disturbed during these short runs in the premonitory period, although the auricular rate is occasionally increased and extra-auricular beats are produced, probably from the contraction of the extra-ventricular beats with retrograde conduction to the auricles.

#### THE CLINICAL MANIFESTATIONS DURING THE PRESENCE OF TRANSIENT VENTRICULAR FIBRILLATION

A major syncopal attack accompanied by convulsive movements of various parts of the body was usually preceded by several shorter periods of unconsciousness as described. If, after a strong beat at the pulse, pallor of the face was noted to follow a few progressively weaker beats with a disappearance of the pulse for at least twenty seconds, then a major attack could invariably be expected.



With this absence of the pulse, when no tremors could be palpated over the precordium and no heart sounds were audible, the respirations would begin to increase in frequency. At first both inspirations and expirations that averaged 40 per minute would be equal in duration. This period usually lasted for about one minute, during which time the patient was totally unconscious, and the face assumed a dark purplish discoloration.

The breathing was noted to become stertorous when the inspiratory phase was almost double the duration of expiration after about one minute following the onset of the attack. It was in this phase of breathing that all the noise (stertorous breathing) could be heard, for the mouth was shut tightly and the air could get in only through the nose which, with the adjacent soft parts of the larynx, would be set into vibration.

After about one and one-half minutes, the muscles of the neck would stiffen, and short jerky movements of the head appeared at the same time that the hands, with both wrists bent over, would be raised involuntarily to the level of the head. Frequently short convulsive seizures would involve practically the whole body. These were accompanied at times by an opening of the eyelids, when the eyes could be seen to rotate in the same directions as the head.

After about two minutes all movements of the body would stop. The inspirations would become extremely labored, as seen usually shortly ante mortem, and the expiratory phase would be slightly increased. At the end of three minutes all breathing would stop. From forty to eighty seconds later, all muscles would relax, and the patient, intensely cyanotic, would appear practically dead.

It was common to observe such periods of unconsciousness last from four to six minutes. Spontaneous revival was usually associated with the appearance of a heart beat and suffusion of the entire skin over the body uniformly, immediately after its appearance. Respirations were not established until from 10 to 20 heart beats could be felt to come through at the wrists. At first the breathing would be shallow and slow, and then within a minute the normal phase would be reestablished progressively as the patient opened her eyes and frequently screamed out loudly, not realizing that she had passed through a phase of unconsciousness.

Her first comments on attaining full consciousness were incoherent and unintelligible, but within ten minutes after the onset of a seizure that would last as long as six minutes she became perfectly rational and always asked to be excused for soiling her linen.

Sometimes, she would immediately lapse into unconsciousness and go through exactly the phases described almost as soon as she was over the effects of one attack.

On several occasions, after the patient had lapsed into unconsciousness and her respirations had ceased for at least two minutes, we attempted artificial respiration. This could never be carried out until her muscles had relaxed completely. It was found possible at such times to push the fingers high up under the left costal margin and, by vigorous massage for about one minute, bring about effectual contractions of the ventricles, to be followed within from twenty to thirty seconds, as a rule, by normal respirations with gradual restoration of consciousness.<sup>4</sup>

#### THE ALTERATIONS IN THE ELECTROCARDIOGRAM DURING TRANSIENT VENTRICULAR FIBRILLATION

Repeated electrocardiograms taken during the syncopal seizures invariably revealed the cardiac mechanism to be due to ventricular fibrillation. A good idea of the type of ventricular oscillations encountered at such times may be gained from the accompanying electrocardiograms (figs 7, 8, 9, 10 and 11). The electrical deflections were extremely variable from time to time. They were aberrant in form and were different in each attack, although they resembled each other closely during the same attack. (For example, compare the deflections in fig 7 with each other and with those in fig 9.)

The height of the electrical deflections varied from a minimal of 0.5 mm (fig 9 *A*) to 15 and 20 mm (fig 8 *Y*). Most of the records revealed a periodic waxing and waning in the height of the oscillations, but occasionally there were sudden and abrupt changes in the mechanism within the same record independent of these variations (fig 9 *B*).

The height of the ventricular complexes during the presence of the basic rhythm preceding a period of ventricular fibrillation seemed to bear some relationship to the height of the oscillations during the presence of ventricular fibrillation. The same is true of the voltage of the complexes of the idioventricular beats following recovery from a period of ventricular fibrillation.

Infrequently some of the waves would seem to be alternately higher, so as to give the impression of electrical alternation (fig 8 *A*, *B*, *C* and *D*).

The frequency of the oscillations varied from 150 to 500 per minute, depending on the height of the waves, for those of greater voltage (fig 8) were also of longer duration individually than those of lower voltage (fig 7 *B*).

Toward the end of each seizure the duration of all the oscillations increased, so that the frequency, as a rule, likewise decreased.

<sup>4</sup> In the light of further experiences we are not certain that massage as carried out by us was responsible for the revival of the heart.

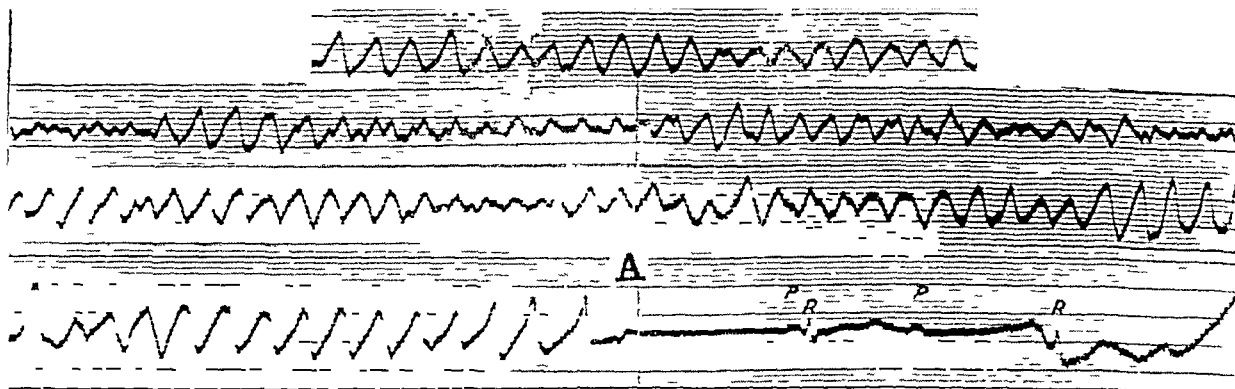


Fig 7—The fibrillatory period A record obtained toward the end of a syncopal seizure lasting more than four minutes The ventricular oscillations are aberrant, there is no definite base line between them, they vary in height, width, shape and form from beat to beat Their frequency is between 200 and 500 per minute There are a periodic waxing and waning of the oscillations throughout the record This transient period of ventricular fibrillation ends with a postundulatory pause (A) and is followed by an intermediary idioventricular rhythm

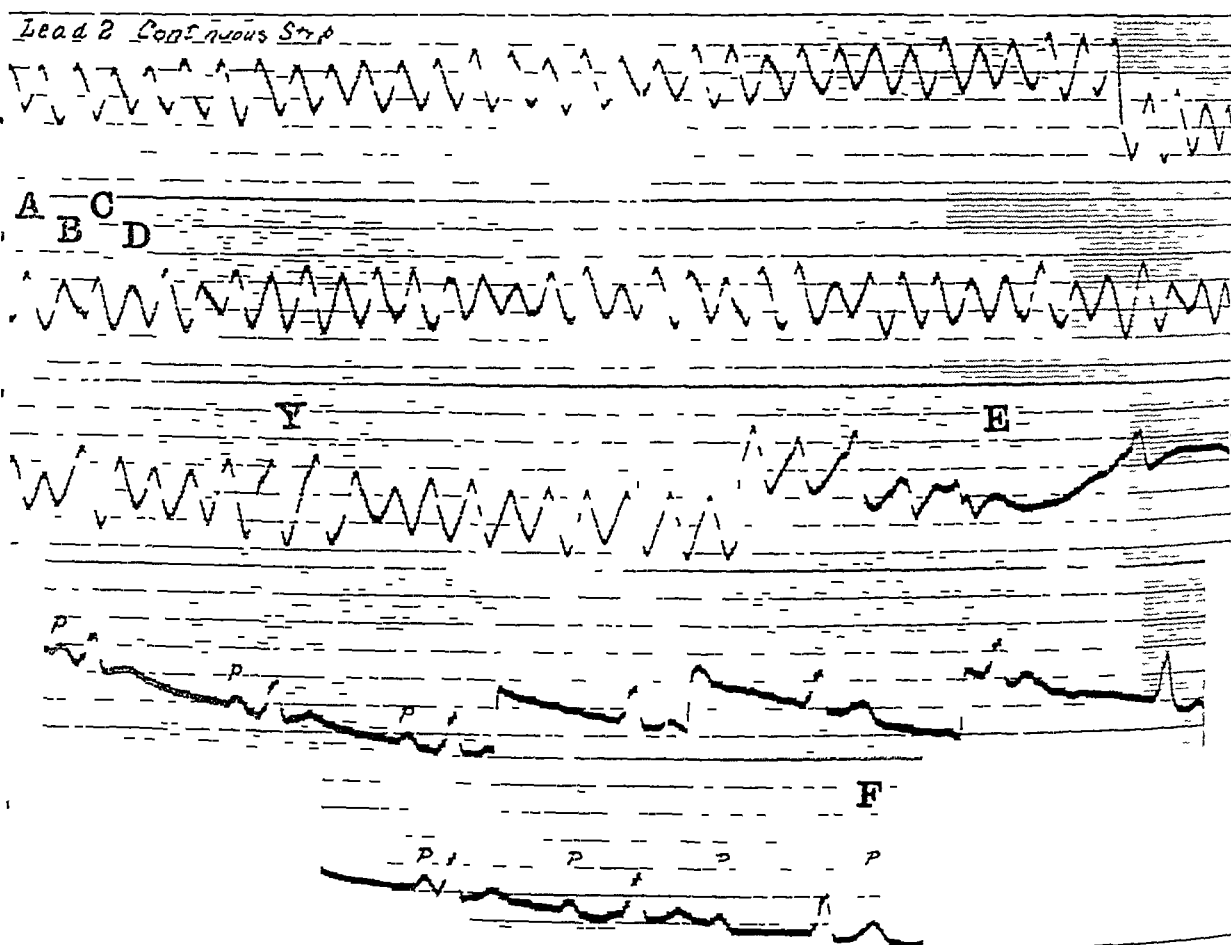


Fig 8—The fibrillatory period A record obtained toward the end of a syncopal attack lasting about three minutes The ventricular oscillations are wide, and at times there is evidence of electrical alternation (A, B, C, D) Their frequency is between 150 and 250 beats Toward the end of the seizure, the complexes increase in height as well as in duration (Y-E) A postundulatory pause (E) is followed by an idioventricular rhythm, with a progressive increase in the ventricular rate from 48 to 136 beats per minute (see fig 15) before there is restoration of the basic rhythm Note that the auricular rate in the postfibrillatory period (E-F) is irregular At times there is no evidence of any auricular contractions

Lead 2 Continuous Strip.

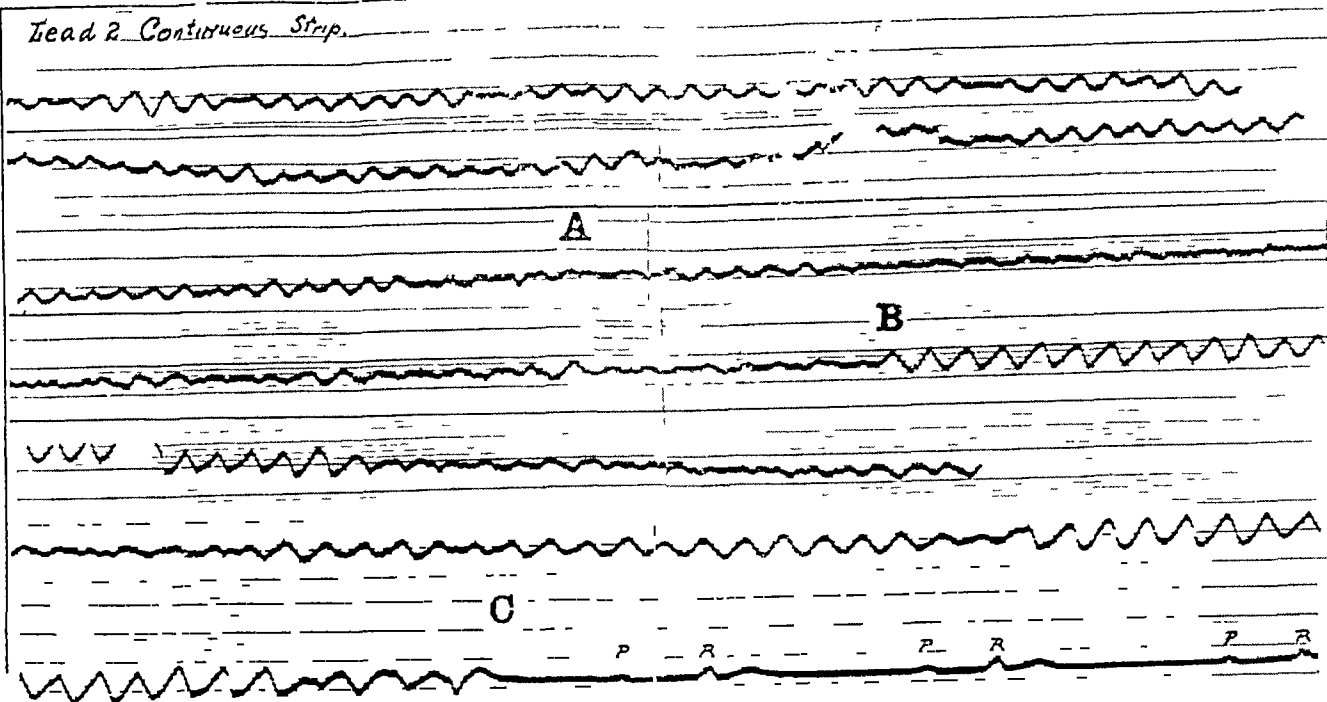


Fig 9—The fibrillatory period A record obtained toward the end of a syncopal attack lasting more than five minutes The ventricular oscillations are of low voltage, with a frequency varying from 200 to 400 per minute Note the periodic waxing and waning in the height of the deflections At B the oscillations are almost regular and resemble each other closely The seizure ends with a postundulatory pause (C) and is followed by an intermediary idioventricular rhythm, with a progressive increase in rate from 25 to 93 beats per minute before there is restoration of the basic rhythm The auricular rate in the postfibrillatory period keeps pace with the ventricular rate

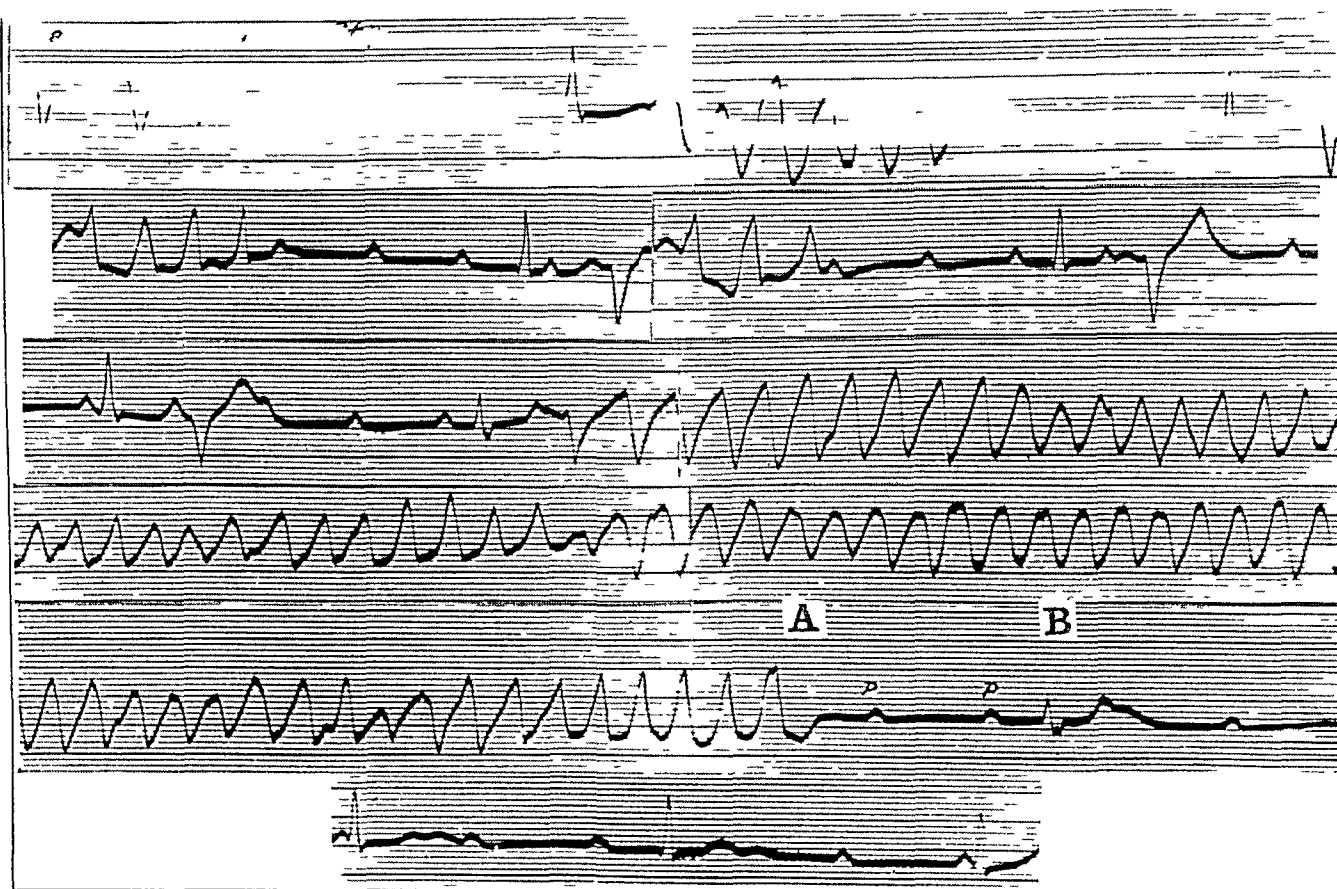


Fig 10—A continuous record, showing a premonitory period followed by a transient seizure of syncope lasting twenty-four seconds The postundulatory pause (A) is followed by 2 auricular beats before the appearance of a single idioventricular beat The basic rhythm follows immediately The auricular sequence is apparently not disturbed during the presence of short runs of ventricular fibrillation

During the longer syncopal seizures, the auricular contractions were not visible, and the mode of recovery from ventricular fibrillation seemed to bear no relationship to their presence, as was observed in the records of another patient<sup>1</sup>

#### THE MODE OF RECOVERY FROM TRANSIENT VENTRICULAR FIBRILLATION

A period of transient ventricular fibrillation ceases promptly and is usually ended by a postundulatory pause, varying in duration from one-half to one and a half seconds (fig 7 *A*, fig 8 *E*, fig 9 *C*, fig 10 *A*, fig 11 *B* and fig 12 *B*). This pause may be followed by 1 (fig 9 *C*), 2 (fig 11 *B* and fig 12 *B*) and sometimes 3 auricular beats before the

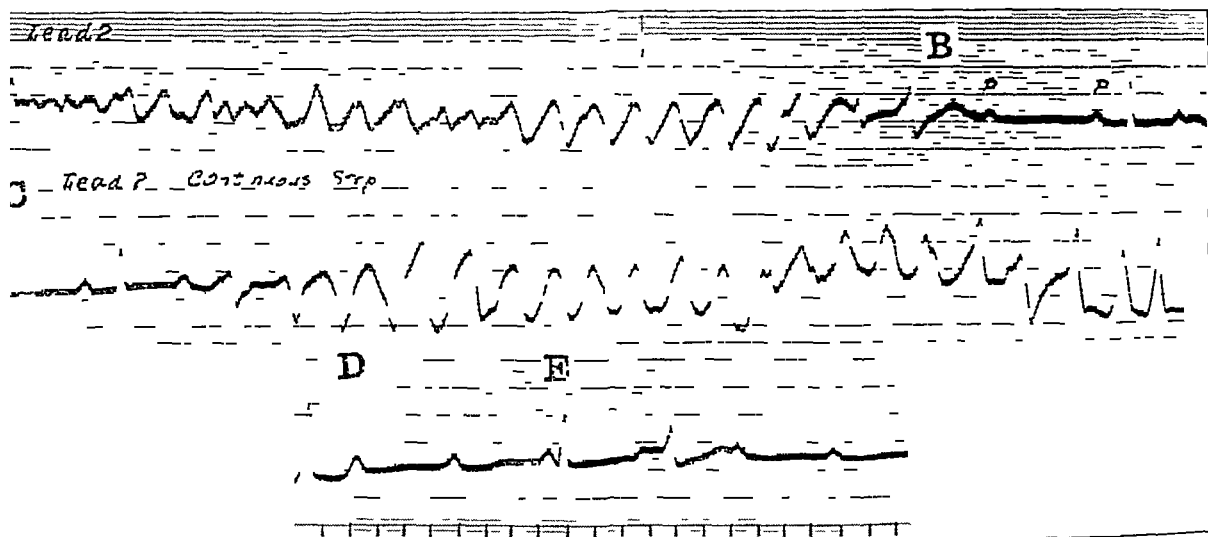


Fig 11—*A*, the end of a syncopal seizure, lasting a little over one minute. *B*, a short postundulatory pause is followed by 2 auricular beats and the basic rhythm is reestablished immediately. *C*, a short period of ventricular fibrillation followed by the basic rhythm (*D-E*) without the presence of a postundulatory pause.

ventricles begin to contract effectually again (11 *D*). Occasionally no auricular contractions may be seen at all preceding such a period of recovery (fig 8 *E*).

The basic rhythm may appear immediately after these initial auricular beats (fig 11 *B* and fig 12 *B*). More often, however, especially if the syncopal seizure has been longer than one minute, an idioventricular rhythm with an irregular rate and complexes totally different from those of the basic rhythm precedes the development of the usual rhythm.

#### THE POSTFIBRILLATORY PERIOD

The end of a major syncopal attack due to transient ventricular fibrillation may be appreciated clinically by the appearance at the radial

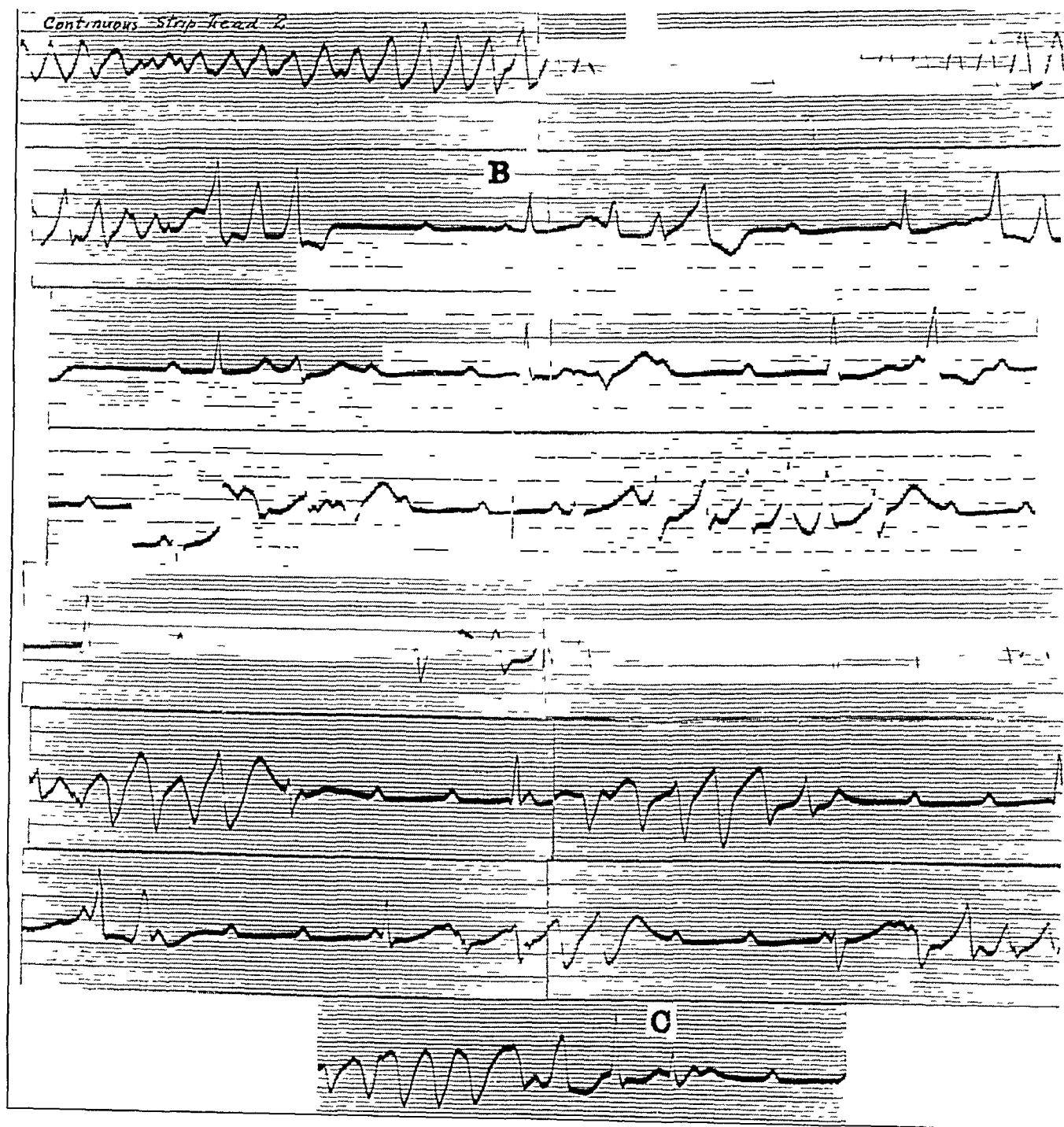


Fig 12—The postfibrillatory period *A*, the end of a syncopal seizure may be followed at times by a series of recurrent groups of ventricular oscillations (*B-C*) resembling the premonitory period (Compare this record with fig 2) As a rule, such records herald the approach of another transient syncopal attack

pulse of a beat that can barely be heard at the apex of the heart. The color of the skin changes immediately after this from a dusky cyanosis to a reddish hue. Beat by beat the sounds become audible at the apex, and the pulse becomes fuller.

The ventricular rate of the intermediary idioventricular rhythm during the period of recovery increases at times progressively from as low as 25 beats per minute at the end of a seizure of ventricular fibrillation to 93 beats, one and a half minutes later (in fig 14 compare *A* to *B* and *C* to *D*) before there is a sudden transition to the usual rate of from 28 to 38 beats per minute (fig 14 *E*). Often the rate of the ventricles during the postfibrillatory period is not as high, averaging

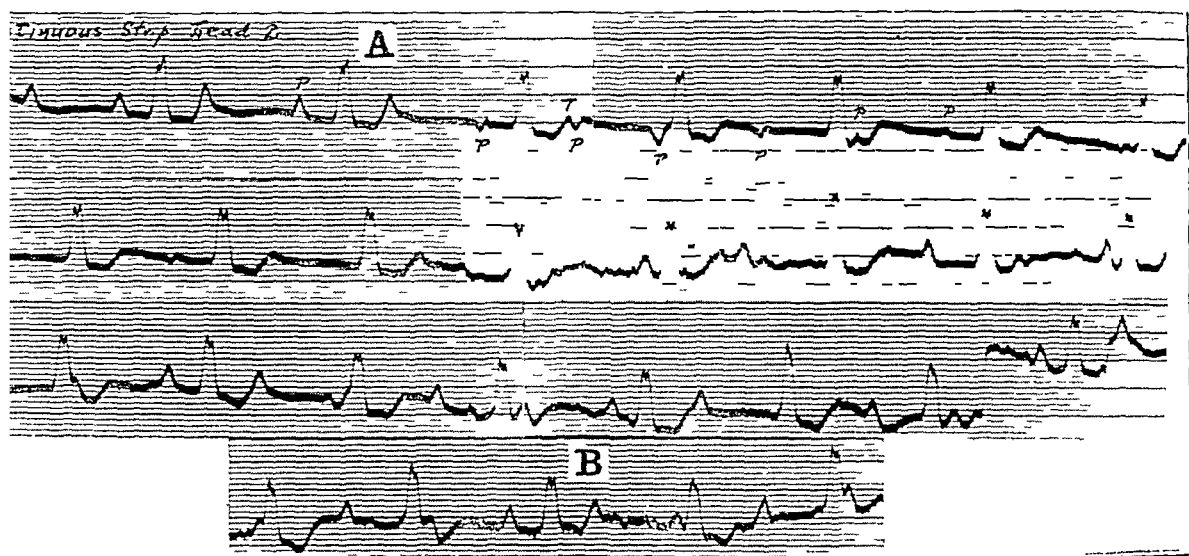


Fig 13—The intermediary idioventricular rhythm obtained fourteen seconds following a long syncopal seizure. The ventricular complexes are aberrant. The ventricular rate increases progressively from 37 to 95 beats per minute. The auricular rate is likewise irregular. At times the auricular complexes are variable in shape, size and form.

only 37 beats (fig 13 *A*), or 48 beats (fig 15 *A*) immediately following the postundulatory pause, and may not reach more than an average of from 50 to 55 beats (fig 13 *B*) before the restoration of the basic rhythm.

Only rarely is a period of "tachysystole" observed during this time, when the ventricular rate may be as high as 136 beats per minute (fig 15 *B*), each beat coming through at the radial pulse, however.

Again the postfibrillatory period may resemble in every respect the period preceding a transient seizure of ventricular fibrillation. (Compare fig 12 *B* to *C* with fig 2 *C* to *E*.)

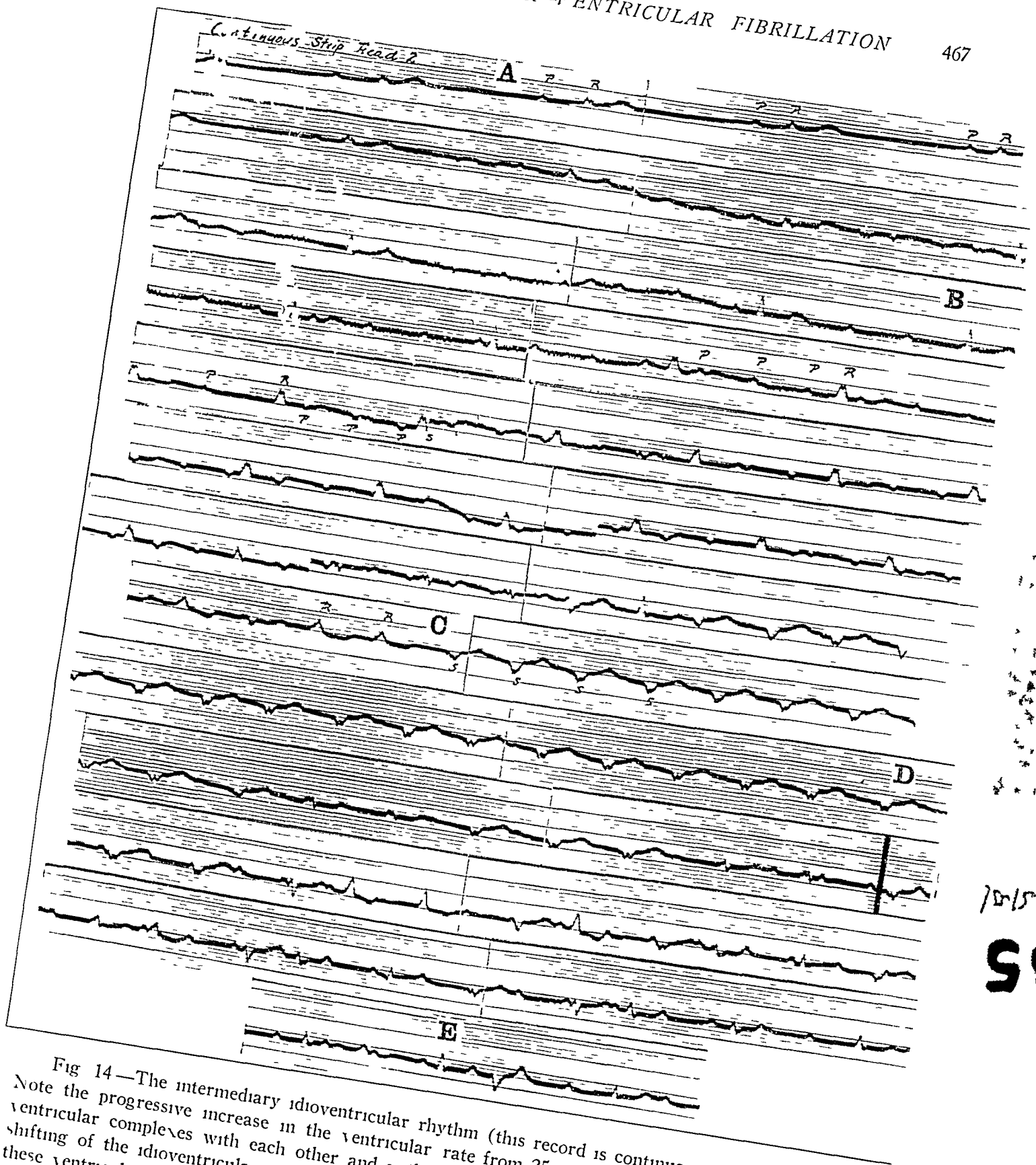


Fig 14—The intermediary idioventricular rhythm (this record is continuous with that of fig 9) Note the progressive increase in the ventricular rate from 25 to 93 beats per minute. Compare the ventricular complexes with each other and with those of the previous record. There is a constant shifting of the idioventricular pacemaker until the restoration of the basic rhythm. The voltage of these ventricular complexes is low as compared with those of figure 13.



The postfibrillatory period usually lasts about one minute, when the normal respiratory sequence is established again and the patient regains full consciousness

The voltage of the ventricular complexes forming the idioventricular rhythm is variable from record to record (fig 13 *A*, fig 14 *A* and fig 15 *A*) and seems to bear some relationship to the size of the electrical deflections during the period of ventricular fibrillation preceding it. These complexes are aberrant in form and vary in the same record

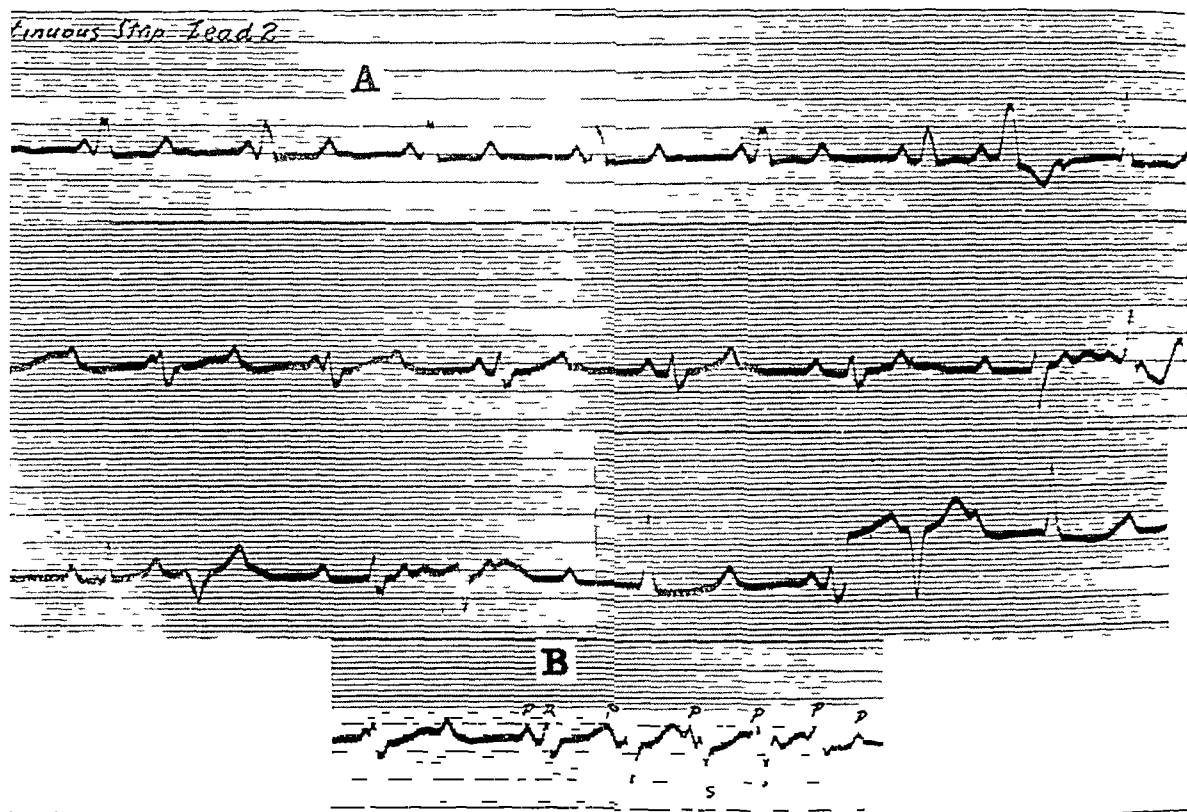


Fig 15—The intermediary idioventricular rhythm shows variable ventricular complexes. Infrequently a "tachysystole" follows one of these attacks when the ventricular rate rises to 136 beats per minute. The auricles keep pace with the ventricles.

(fig 14 *A*, *B* and *C* and fig 15 *A* and *B*), indicating a change in the pacemaker of the ventricles until the reestablishment of the basic rhythm.

During this period the auricles may keep pace with the ventricles (fig 15 *B*), or the P waves may be totally absent (fig 8 *E* and *F* and fig 14 *C*). Often they too show a change in their pacemaker (fig 13 *A*), but their presence or absence seems to bear no relationship to the return to normal of the basic ventricular rate.

## SUMMARY

1 A clinical and electrocardiographic study was made of the syncopal seizures in a patient with auriculoventricular dissociation. More than a hundred electrocardiograms obtained during such seizures revealed the cardiac mechanism to be due to transient ventricular fibrillation.

2 The natural periods of transient ventricular fibrillation in this patient have varied in duration from only a few seconds to six minutes each, and as many as two hundred and seven attacks of unconsciousness have been observed during a period of twenty-four hours with spontaneous revival. During a period of four months' observation, not a single day passed without the patient experiencing at least one attack.

3 The premonitory periods preceding a transient seizure of ventricular fibrillation of the ventricles have been variable. They consisted at first of alternate premature beats of the ventricles, which increased the basic ventricular rate. These were followed shortly by irregular periods of recurring groups of aberrant ventricular oscillations, only the first few of which could be heard at the apical region of the heart or felt at the radial pulse.

4 Pallor of the face and momentary loss of consciousness followed the appearance of these recurrent groups of ventricular oscillations when, during their presence, the pulse disappeared for more than eight seconds but for not more than twelve.

5 A major attack of unconsciousness with cyanosis, stertorous breathing and convulsions took place when the heart sounds and pulse disappeared for at least twenty but not less than forty seconds. The electrocardiograms made during these periods invariably revealed ventricular fibrillation.

6 The frequency of the ventricular oscillations during the periods of transient ventricular fibrillation varied from 250 to 500 per minute.

7 Spontaneous revival from a seizure of ventricular fibrillation was usually ushered in by the appearance in the electrocardiograms of a postundulatory pause, which was followed by an intermediary idioventricular rhythm, as a rule, with an increasingly irregular rate before the restoration of the basic ventricular rhythm.

8 It is important to appreciate that syncopal seizures in patients with auriculoventricular dissociation are much more commonly associated with transient periods of ventricular fibrillation than has been suspected hitherto.

9 Rational therapy for the prevention of syncopal seizures in patients with auriculoventricular dissociation depends on an intimate knowledge of the cardiac mechanism underlying these seizures.

# LOCALIZATION OF AFFERENT VISCERAL IMPULSES IN THE SPINAL CORD

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In 1922, one of us (S W ) and Hatcher<sup>1</sup> located two small symmetrical areas on the floor of the fourth ventricle in cats, corresponding to the sensory nuclei of the vagus nerves. The application of unusually small amounts of certain drugs to these areas promptly induced nausea and vomiting, whereas local depression by drugs or mechanical injury abolished this response. This finding indicated that the sensory nuclei of the vagi are essential to the mechanism of vomiting, whether of central or peripheral origin. It was further shown that vomiting could be induced by peripheral stimulation of a viscus after vagotomy or by stimulation of an organ not supplied by the vagus nerve.<sup>2</sup> These observations indicated that both the vagus and the sympathetic fibers of the autonomic nervous system carry afferent impulses to the so-called vomiting center, and that vomiting can be induced reflexly through either path. The concept that the autonomic nervous system is subdivided into a sympathetic and a parasympathetic system seemed, therefore, to be as justifiable for the sensory part of the autonomic nervous system as Langley<sup>3</sup> has suggested it is for the motor portion. Hatcher and one of us (S W )<sup>4</sup> further demonstrated that vomiting is always a reflex that is induced (1) by the local action of physical or chemical

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1 Weiss, S, and Hatcher, R A. Localization of the Vomiting Center, *Proc Soc Exper Biol & Med* **20** 310, 1922

2 Weiss, S, and Hatcher, R A. The Mechanism of the Vomiting Induced by Antimony and Potassium Tartrate (Tartar Emetic), *J Exper Med* **37** 97, 1923

3 Langley, J N. The Autonomic Nervous System, Cambridge, England, W Heffer & Sons, Ltd, 1921, part 1, pp 1 and 28

4 Hatcher, R A, and Weiss, S. Studies on Vomiting, *J Pharmacol & Exper Therap* **22** 139 1932

agents on the center, which is excited to such an extent that normal afferent impulses produce a reflex discharge of the motor impulses characteristic of vomiting (central vomiting), or (2) by the action of abnormal peripheral impulses on the center which is stimulated to discharge impulses that produce vomiting (peripheral vomiting)

These facts suggested that severance of the afferent path at any point would abolish vomiting and that the presence or absence of the vomiting response could be used as an index of the integrity of the afferent path. The present study was therefore undertaken with the hope that this method would localize the afferent path of the vomiting reflex in the spinal cord, and that this path would suggest, possibly, the site of other afferent visceral tracts and offer a new approach to the study of this aspect of the autonomic nervous system

#### METHOD OF INVESTIGATION

Vomiting induced by digitalis bodies was selected as an experimental reflex suitable for use in determining the seat of afferent impulses in the cord, as this mechanism had been studied in detail by Hatcher and one of us (S W) <sup>5</sup>. It was shown that large doses of digitalis bodies applied locally to the vomiting center in the medulla of cats did not produce vomiting as did other emetics, such as nicotine and apomorphine hydrochloride. In contrast, a single intravenous dose of digitalis produced prolonged nausea and vomiting. It was pointed out that vomiting produced by digitalis poisoning is a reflex the peripheral seat of action of which is in the heart or its adjacent structures. This concept was further substantiated by perfusion experiments in which the intact brain was essentially excluded from the heart and trunk. When the brain so prepared was perfused with defibrinated blood containing ouabain, vomiting did not occur, but when the same animals were given intravenous injections of ouabain, which was prevented from reaching the medulla, emesis resulted. Furthermore, it was demonstrated that vomiting caused by digitalis was abolished soon after complete denervation of the heart, and that the same abolition of vomiting occurred after large doses of nicotine <sup>6</sup>. Complete section of the cord at the level of the first thoracic vertebra in vagotomized cats also prevented vomiting. Section in this region of the cord would, of course, intercept fibers coming from the heart through the inferior cervical sympathetic ganglion and passing to the medulla through the cervical cord.

<sup>5</sup> Hatcher, R. A., and Weiss, S. The Seat of the Emetic Action of the Digitalis Bodies, *Arch Int Med* **29** 690 (May) 1922, Reflex Vomiting from the Heart, *J A M A* **89** 429 (Aug 6) 1927, The Seat of the Emetic Action of the Digitalis Bodies, *J Pharmacol & Exper Therap* **32** 37, 1927

<sup>6</sup> Hatcher and Weiss (footnote 5, third reference)

## TECHNIC

All experiments were carried out on adult cats, which were anesthetized with ether. To intercept any impulses that might make their way to the cord through the stellate ganglions, the spinal cord was selectively injured in the region of the fifth and sixth cervical vertebrae. Double vagotomy was performed, and tracheal cannulas were inserted. The cervical vertebrae were then exposed. With the aid of bone rongeurs the spinous processes of the fifth or sixth cervical vertebra were removed. The cord was gently moved to the side and the lamina of the vertebra removed laterally to the transverse processes on both sides. This method of exposure was sufficient for injury to the dorsal and lateral columns of the spinal cord. To section the anterior column, it was necessary to cut off the anterior arches of the vertebrae and expose as much of the ventral surfaces of the cord on each side as possible. In the first experiments, involving injuries to the anterior column, one section was made on each side of the anterior fissure. This was rather unsatisfactory, for it was difficult to gauge the extent of the damage, and it was important that the damage on both sides should be symmetrical. Furthermore, the removal of both anterior arches increased operative shock and hemorrhage which, when extensive, left the animals depressed. A depressed animal generally fails to vomit after any powerful emetic. This first technic was then modified to the exposure of the lamina, transverse processes and the arch of the vertebra on one side only, and a single anterior section was made with a specially shaped knife. Hemorrhage from veins about the spinal cord was controlled by very light pressure. The hemorrhage was slight in some experiments, and considerable in others. Massive local hemorrhage and subsequent depression excluded the use of an animal in these experiments. In each experiment the subdural and subarachnoid spaces were opened, and the spinal fluid was allowed to escape. After the injury was inflicted, the dura was approximated and the muscle layers and skin were carefully closed and sutured. The animals were then placed in a warm cage for recovery. When the operative procedure and duration of anesthesia were relatively short, i. e., less than one and a half hours, and attended with slight hemorrhage, the animals were generally in good experimental condition within three or four hours. Their condition was studied by noting spontaneous movements, alertness and reactions to visual and auditory impressions and pain stimuli. When such observations showed that the general condition of the animals was satisfactory, a fatal dose of one of the digitalis bodies was given intramuscularly, and the animal was kept under constant observation for signs of nausea or vomiting, which almost regularly precede death from digitalis in animals in good condition.<sup>7</sup> From 10 to 20 cc. of the tincture of digitalis or from 3 to 6 mg. of strophanthus was injected into the gluteal muscle. This dose was repeated, and the animal was watched until death from digitalis poisoning supervened. It was repeatedly observed that the intramuscular absorption of digitalis bodies was slower after injuries to the spinal cord. Following the death of the animals the cord in the region of the injury was carefully removed and lampblack applied to the site of the injury to make identification easier. The spinal cords were placed in 10 per cent formaldehyde and serial sections made. After the section had been stained, a composite diagram was made of the extent of the injury. Injuries consisting of narrow, stablike wounds, which involved the posterior column with

7 In an earlier group of experiments an effort was made to study vomiting induced by gastric irritants, such as corrosive mercuric chloride. However, the passing of the stomach tube with its attendant excitement after the extensive operative procedure was often sufficient to cause a subsequent inhibition of vomiting. This procedure was then abandoned, and digitalis in the form of a tincture or a solution of strophanthus was regularly used.

the tracts of Goll and Burdach, often did not gap, and it was therefore difficult to gauge the extent of damage in such experiments. In some experiments, indeed, there was such complete reapproximation of the two injured surfaces that the injury could not be identified in the serial sections. Injuries to the lateral and ventral columns usually showed an unmistakable gap.

### RESULTS

Twenty-four experiments were performed on adult cats. Complete transverse section of the cervical and upper thoracic spinal cord was first carried out in control experiments to be sure that the afferent sympathetic impulses did traverse the spinal cord, and that its section would prevent their transmission. The condition of six animals used for this test was good approximately four hours after the operative procedure. In five of the animals the section ran transversely between the fifth and sixth cervical vertebrae, in one, at the level of the second thoracic vertebra. Vomiting did not occur after the administration of fatal doses of digitalis to these animals. It seems probable that the absence of vomiting was not due to depression.

Complete sections of the posterior column were performed in ten animals, and were satisfactory for analysis. In seven there was definite vomiting or retching before the typical digitalis death. In one, there was unmistakable evidence of nausea approximately one minute before the final convulsion. The animal licked his lips rapidly, a characteristic sign of the nausea associated with vomiting.<sup>4</sup> No evidence of nausea or vomiting appeared in two of the ten animals. In one the injury was found to involve more than the posterior column, with evidence of pyramidal paralysis as well as posterior column ataxia. There was no explanation for the other animal's failure to vomit. The animal was apparently in good condition, and died a typical digitalis death. In operating on this animal great care had been taken to confine the incision to the posterior column, but it is possible that the tip of the blade penetrated more anteriorly than could be determined from the serial section. All ten animals showed the usual responses to pain stimuli. The results of these experiments showed that the posterior column does not contain the path that carries the afferent impulses responsible for digitalis vomiting. The protocols of two typical experiments follow.

EXPERIMENT 33—Dec 10, 1926 Male cat, weight 2.6 Kg

- 2 50 p m Ether anesthesia started
- 3 20 p m Spinous processes and lamina up to the lateral vertebrae removed, and section of the posterior columns of Goll and Burdach completed
- 3 30 p m Muscle layers and skin sewed
- 3 45 p m Double vagotomy, with insertion of tracheal cannulas, performed
- 4 15 p m Animal out of anesthesia
- 8 15 p m Animal in excellent condition. Responded to call promptly. Ran across floor with weakness of the hind legs and with ataxia. Attempted to escape from room. Pain responses present
- 8 21 p m 10 mg of strophanthin per kilogram given intramuscularly

- 8 58 p m Rapid breathing started  
 9 01 p m Animal moved about  
 9 02 p m Respiration suddenly slowed down, and typical retching movements of vomiting developed  
 9 13 p m Animal died

Cord removed and sectioned serially. Result of composite injuries of the section indicated that section involved the posterior column of Goll and Burdach and adjacent pyramidal tracts. One of the sections is reproduced in figure 1.

EXPERIMENT 36—Jan 15, 1927 Male cat, weight, 27 Kg

- 2 45 p m Ether anesthesia started  
 3 00 p m Spinous processes and laminae of the sixth and seventh cervical vertebrae removed and cord exposed  
 3 25 p m Rather extensive posterior section of the Goll and Burdach column, probably involving adjacent structures



Fig 1—Injury of the posterior column of the spinal cord in experiment 33. This and more extensive injuries did not prevent vomiting.

- 3 30 p m Tracheotomy performed, cannula inserted, double vagotomy performed  
 6 00 p m Animal answered call quickly, lifted head, but was unable to stand on four legs  
 6 10 to 7 10 p m Twenty milligrams of ouabain given in divided doses. Immediately after each injection, the animal struggled with considerable excitement, indicating pain reaction.  
 6 50 p m Retching movements of the thorax and abdomen  
 6 55 p m Retching movements again  
 7 15 p m Typical digitalis convulsions and death

Cord removed. Lampblack dusted into the sectioned area. Composite study of serial section indicated that injury involved almost the entire posterior half of the cord, extending anteriorly over the central canal. A section typical of this group is shown in figure 2.

Portions of the lateral columns of the spinal cord were sectioned in five animals. In all five there was typical digitalis vomiting. In two additional instances the condition of the animals was considered only fair. After the injection of digitalis, these two animals showed an unusual degree of excitement and respiratory stimulation. Vomiting did not occur in either. It is possible that the excitement, with its attendant respiratory stimulation, was the cause of the inhibition. It has been shown by Openchowski<sup>8</sup> that rapid respiration inhibits vomiting. Previous observations<sup>4</sup> indicated that rapid respiration, pain and scratch reflexes are also capable of inhibiting the vomiting reflex. In this group of experiments, in spite of extensive injury which involved the lateral cerebellar and pyramidal tracts, vomiting was not prevented. It was clear, therefore, that injury to a large part of the cord in itself was not sufficient to inhibit vomiting.

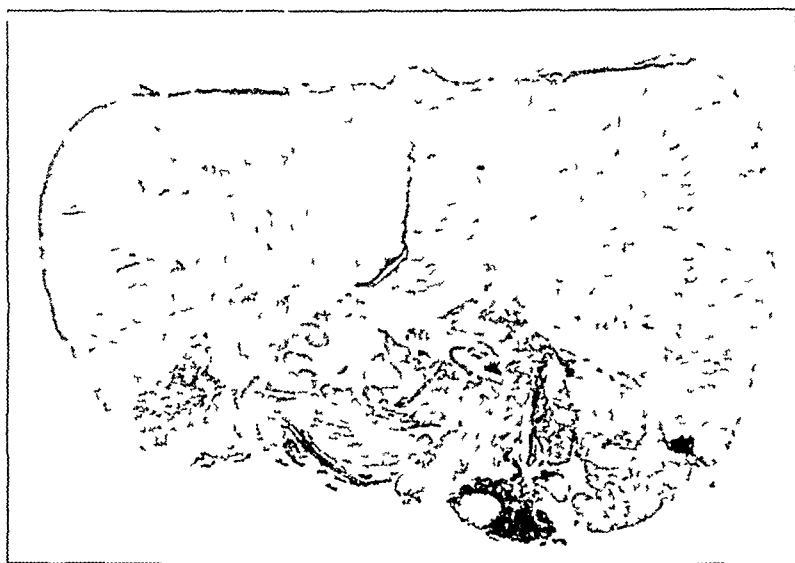


Fig 2—Injury of the posterior column of the spinal cord in experiment 35. This type of injury did not prevent vomiting.

These experiments indicated that the path of vomiting was not in the lateral columns. A protocol of a typical experiment follows:

EXPERIMENT 30—Nov 14, 1926 Male cat, weight 3 Kg

2 12 p m Administration of ether started

2 20 to 2 40 p m Posterior lamina of the seventh cervical vertebra removed. Practically no bleeding.

3 01 p m Lateral sections in the region of the seventh cervical vertebra made. Small amount of spinal fluid escaped.

8 20 p m Animal in fairly good condition. Crawled on his stomach with a certain amount of ataxia. Attempted to climb into a chair.

8 23 p m Tincture of digitalis, 3 cc, injected.

8 35 p m Animal in good condition, crawled about. At times attempted to run across the room.

<sup>8</sup> Openchowski, T. Ueber die nervösen Vorrichtungen des Magens, *Zentralbl f Physiol* 3 1, 1889.



- 9 04 p m Tincture of digitalis,  
 9 18 p m Definite signs of nausea  
 9 20 p m Typical retching move.  
 9 22 p m Retching and vomiting  
 9 24 p m Convulsions and typical digit

and typical retching movements

Following death, cord was carefully removed and  
 Composite diagram indicated that lateral columns up  
 on both sides. Level of injuries was not exactly the same  
 figure 3, which shows one of the sections of cord, only  
 visible

aries of the section  
 and Burdach and  
 figure

The anterior columns were sectioned in thirteen animals. The main part  
 in these experiments involved mainly the sensory pathways running  
 side the anterior pyramidal tract in the anterior and lateral aspect of the

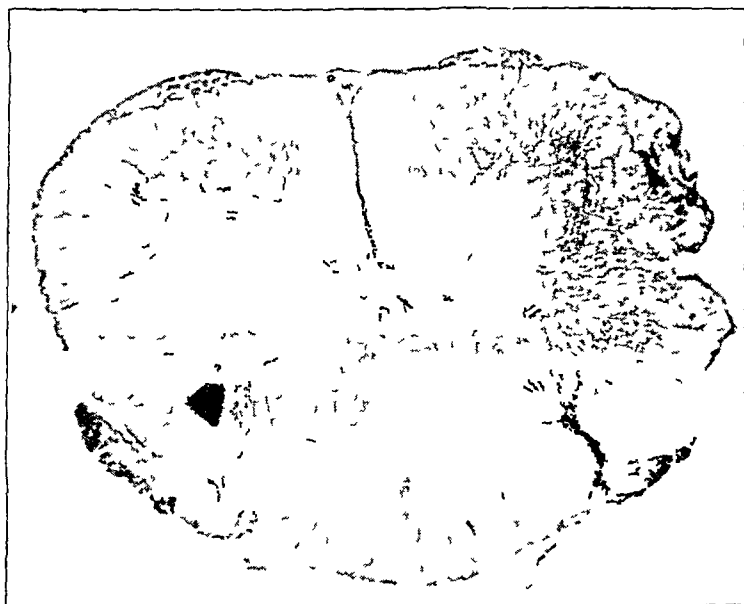


Fig 3—Injury of the lateral column of the spinal cord in experiment 30. This section shows part of the injury to the right lateral column. The similar injury to the left lateral column was not inflicted at exactly the same level and hence is not visible. This type of injury did not inhibit vomiting.

anterior column. The fibers of these areas have been shown to carry pressure, temperature and pain sensations.<sup>9</sup> In nine of these experiments vomiting failed to occur, although the animals were in excellent condition. In four instances there was unmistakable vomiting. Two lateral incisions had been made in these cases with the earlier technique, and the serial sections showed these to be incomplete as far as destruction of the entire anterior columns was concerned. The explanation for the presence of vomiting in these experiments was therefore obvious. In

<sup>9</sup> Petren, K. Ueber die Bahnen der Sensibilität im Rückenmark besonders nach den Fällen von Stickverletzung studiert, *Arch f Psychiat* **47** 495, 1911.  
 Rothman, M. Zur Frage der Sensibilitätsleistung im Rückenmark, *Deutsche Ztschr f Nervenhe* **43** 433, 1912.

Portions of lateral columns of spinal cord in which vomiting was abolished, it was found that in all five the injury was typical of the lateral portions of the anterior column. The conclusion of the animal experiments was that with one stroke of the knife the response to digitalis, the strychnine convulsion, and the reflexes of the anterior columns of the cord follow.

It is possible that the injury was not complete. Female cat, weight, 3.4 Kg.

March 24, 1927. Usual median line incision posteriorly. Muscle separated from both sides of the vertebral body canal. Sixth and seventh spinous processes removed. On the left side the lateral body wall to the median anterior line removed, thus removing one half of the spinal cord. Anterior portion of the cord sectioned.

6 50 p m Tracheotomy and double vagotomy performed.

9 45 p m Animal in good general condition. Lifted self up and moved to opposite end of cage with ataxia.

10 10 p m Strophanthin, 5 mg, injected intramuscularly.

10 20 p m All pain responses abolished. Rather restless.

10 35 p m Urinary incontinence and excitement.

10 36 p m Death.

Cord removed and serially sectioned. Histologic examination indicated that injury involved anterior and anterior lateral columns. One of the sections is reproduced in figure 4.

EXPERIMENT 59—March 24, 1928. Cat, weight, 2.58 Kg.

6 35 p m Ether anesthesia started. Cord exposed as in experiment 53. Section of anterior column of the cord. Vagotomy and tracheotomy.

7 30 p m Operation completed.

9 00 p m Animal in good condition. Moved all four extremities, but was unable to walk because of marked ataxia, crawled about. Strophanthin, 3 mg, injected intramuscularly.

9 24 p m Animal had typical digitalis convulsion and died without any evidence of nausea or vomiting. Serial section indicated that injuries involved anterior and lateral columns. One section of the cord with injury is reproduced in figure 5.

The failure of severance of both the posterior and the lateral columns to abolish the vomiting produced by digitalis points to the anterior column as the pathway of afferent impulses. The abolition of vomiting by section of the anterior column further confirms the localization in this region of the spinal cord.

#### COMMENT

The autonomic nervous system hitherto has been regarded largely as an efferent system. Langley,<sup>3</sup> in defining the autonomic nervous system, said "The autonomic nervous system consists of nerve cells and nerve fibers, by means of which efferent impulses pass to the tissues other than multi-nuclear striated muscle." Later he also stated "The facts show that there is a close relation between the action of the drug and the innervation of sympathetic and parasympathetic nerves respectively and they suggest that there is a fundamental difference between the two systems."

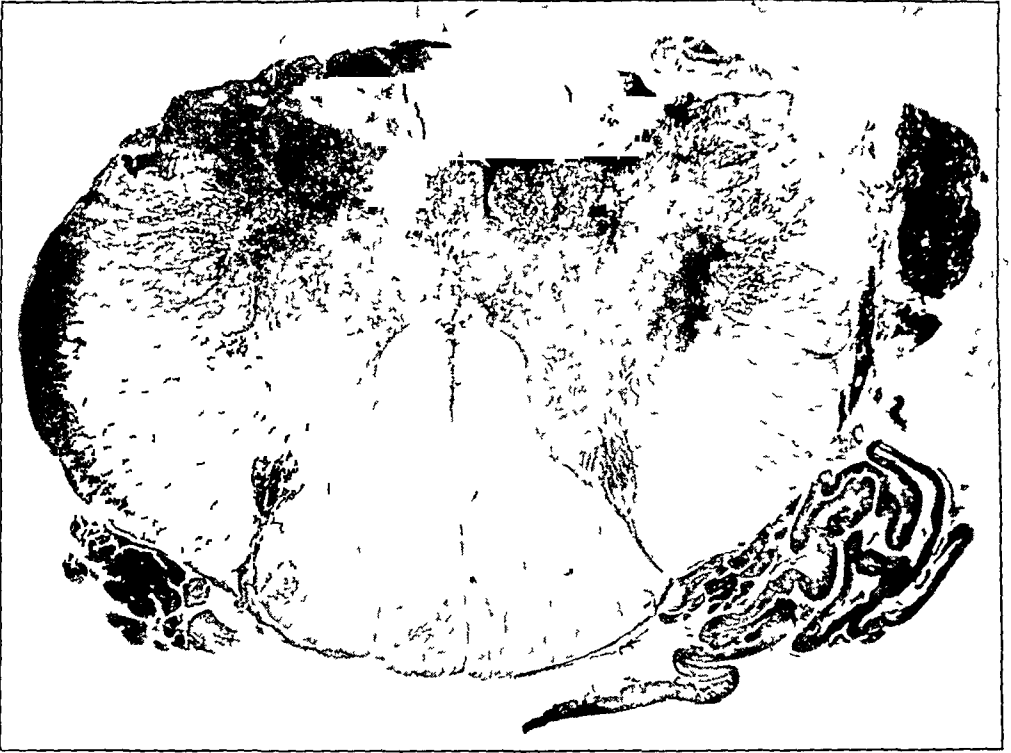


Fig 4—Injury of the anterior column of the spinal cord in experiment 53 This and less extensive injuries inhibited vomiting



Fig 5—Injury of the anterior column of the spinal cord in experiment 59 This injury inhibited vomiting

Hatcher and one of us (S W), in 1923,<sup>4</sup> summarizing experiences with the afferent visceral impulses involved in vomiting, stated "The results of our experiments indicate that the efferent fibers concerned with emesis may be classified as sympathetic and parasympathetic with as much reason as the afferent, for atropine, pilocarpin and ergotoxin induce impulses which traverse these just as selectively as they act on the efferent end apparatus." The results of the present study indicate that both sympathetic and parasympathetic visceral afferent impulses induced by digitalis *bitteris*, and perhaps by other emetics, enter the cord through the sympathetic chain and run up to the higher sympathetic centers in the anterior column.

In 1926, Spiegel<sup>10</sup> reported that the inhibition of respiration produced through dropping a concentrated barium chloride solution on the stomach and small and large intestine or through electric stimulation of the splanchnic nerve cannot be prevented by bilateral section of the posterior columns of Goll and Rudach or of the cerebellar tracts. This respiratory inhibition is abolished, however, by sectioning the anterior column or the anterior aspects of the lateral columns. His experiments are therefore in harmony with our observation that the visceral efferent impulses run in the anterior and lateral portion of the anterior column. Whether these afferent impulses are carried within narrowly definable tracts or traverse a relatively wide area cannot be stated. It is of interest, however, that the same area of the cord carries the visceral afferent impulse to the vomiting and respiratory centers and the somatic afferent sensations of touch, pain and temperature. Our previous observations<sup>11</sup> show that afferent cutaneous impulses have a close relationship to the mechanism of visceral pain, and that visceral pain induced by abnormal afferent sympathetic impulses may cease completely if the corresponding afferent impulses from the skin are blocked. These facts suggest that the close relationship between the autonomic and somatic afferent impulses in the spinal cord is not only structural but also functional.

#### SUMMARY AND CONCLUSIONS

- 1 The pathway of the afferent impulses of the vomiting reflex is located in the centripetal tracts of the anterior column of the spinal cord.

- 2 A close structural and functional relationship between afferent visceral and certain afferent somatic impulses in the spinal cord is suggested.

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<sup>10</sup> Spiegel, E. A. Experimentelle Grundlagen zur Chordotomie, *Deutsche Ztschr. f. Nervenhe.* 89:18, 1926.

<sup>11</sup> Weiss, S., and Davis, D. The Significance of the Afferent Impulses from the Skin in the Mechanism of Visceral Pain, *Am. J. M. Sc.* 174:517, 1928.

# DIURETIC EFFECTS AND CHANGES IN BLOOD AND URINARY METABOLITES AFTER DIGITALIS IN NORMAL AND IN EDEMATOUS PERSONS

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In recent experimental and clinical studies of diuretics, much attention has been devoted to correlation of quantitative changes in blood and urinary metabolites, especially the chlorides, with the object of determining the seat of diuretic action. The significance of the correlations has been about as follows: simultaneous increases in blood and urinary chlorides and in the output of urine reflect a direct and general action of the diuretic on the tissues, whereas a reciprocal change in the blood and urinary chlorides, i. e., a decrease in blood chlorides with a simultaneous increase in urinary chlorides and an increase in the output of the urine, reflect indirect effects through circulatory or renal changes, or both. These effects have been described for a number of diuretics, chemically and pharmacologically different. For instance, Hartzieganu, Gavrilă and Borbil<sup>1</sup> demonstrated concurrent increases in blood and urinary chlorides during diuresis after mersalyl and merbaphen, in healthy and edematous human subjects. The same phenomena have been observed in healthy dogs and rabbits by Lyons,<sup>2</sup> using merbaphen, and by Curtis,<sup>3</sup> using theophylline. Lie<sup>4</sup> reported increases in the urinary chlorides during diuresis in a normal human subject receiving caffeine, but Lie did not investigate the blood chlorides. I have previously reported that bismuth sodium tartrate, merbaphen, mersalyl and theophylline, administered to human subjects,<sup>5</sup> and bismuth

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Supported, in part, by a grant from the Rockefeller Fluid Research Fund of the School of Medicine, Stanford University

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1 Hartzieganu, I., Gavrilă, I., and Borbil. *Compt rend Soc de biol* **99** 1813, 1928

2 Lyons, R. *M Clin North America* **12** 1341, 1929

3 Curtis, G. M. *Action of Specific Diuretics*, *J A M A* **93** 2016 (Dec 28) 1929

4 Lie, E. *Am J Physiol* **92** 619, 1930

5 Hanzlik, P. J., Bloomfield, A. L., Stockton, A. B. and Wood, D. A. *J A M A* **92** 1413, 1929. Stockton, A. B. *Proc Soc Exper Biol & Med* **27** 721, 1930

given to rabbits,<sup>6</sup> caused simultaneous increases in the chlorides of the blood and urine during diuresis, the chlorides were generally unchanged in the absence of diuresis. The increase in urinary chloride was often not only an increase in the absolute daily amount, but actually an increase in concentration. Hence it appeared that these diuretics acted directly on the body tissues, mobilizing chloride and water.

About the only other useful diuretic that has not been investigated in the light of the newer theories of diuretic action is digitalis. Cushny<sup>7</sup> suggested the desirability of studies on the effects of digitalis on metabolites. Recently, an attempt in this direction appears to have been made by Kellum and Keith,<sup>8</sup> but the results obtained on metabolites are not given in the abstract; they report only a variability in diuretic response and suggest the advisability of using other diuretics with digitalis in order to obtain satisfactory diuresis. In another abstract, Keith<sup>9</sup> stated that he has compared the changes in  $p_{\text{H}}$ , volume, chloride, total fixed base and nitrogen in urines of twelve normal men who received the following diuretics: digitalis, sodium nitrate, urea, sucrose, organic mercury compounds and theophylline-ethylenediamine and the chloride, nitrate and acetate of ammonium. It is stated that the diuretic effects were most marked after organic mercury and the chloride and nitrate of ammonium, and minimal after digitalis and ammonium acetate; the changes in metabolites are not mentioned. Experimentally, Hirsch<sup>10</sup> demonstrated increases in urinary chlorides, but no changes in blood chlorides in rabbits receiving various digitaloids, especially scillaren. Gremels<sup>11</sup> studied the actions of digitalis and various digitaloids on the heart-lung-kidney preparation; these drugs caused an increased excretion of water and chloride in the urine, but no increase of total nitrogen. Unfortunately, changes in the blood chlorides were not observed.

These various results on animals and on an excised system of organs suggest that digitalis, as a diuretic, acts differently than do the purines and metals. The conditions in normal animals, and in an excised organ system largely free of tissues, are not comparable with the conditions in which digitalis is used as a diuretic, namely, in edema of cardiac origin. While it is logical to expect that the diuretic action of digitalis would manifest itself for the most part through circulatory improvement, yet unexpected variations in the drug's action are a matter of common knowledge and a tissue action could not be finally excluded.

6 Stockton, A. B. *Arch. internat. de pharmacodyn. et de therapie* **51**, 52, 1931.

7 Cushny, A. R. *The Action and Uses in Medicine of Digitalis and Its Allies*, New York, Longmans, Green & Company, 1925.

8 Kellum, E. L., and Keith, N. M. *J. Clin. Investigation* **10**, 667, 1931.

9 Keith, N. M. *J. Pharmacol. & Exper. Therap.* **42**, 260, 1931.

10 Hirsch, H. *Arch. f. exper. Path. u. Pharmacol.* **160**, 220, 1931.

11 Gremels, H. *Arch. f. exper. Path. u. Pharmacol.* **157**, 92, 1930.

until the question was tested. Therefore, it appeared desirable to make a study of the quantitative changes in metabolites of the blood and urine after digitalis in normal and edematous human subjects along similar lines as in previous studies of bismuth.<sup>5</sup> In addition to the chlorides, the changes in uric acid and sugar of the blood and urine were observed. It was thought that the changes in endogenous uric acid would reflect more direct and intimate actions of the drug on the tissues, as the result of effects on cellular or nuclear metabolism. Less was expected from the changes in dextrose on account of the uncontrolled carbohydrate intake and liver glycogen, although the observations were made for any results that might serve as supplementary evidence. Briefly, the clinical results obtained sustain the results of Hirsch and of Gremels on animals, and indicate that the mechanism of digitalis-diuresis is different from that of the puines and the metals.

#### METHODS

In all, twelve patients were used in this study. They were divided into four groups representing different conditions.

*Normal*—Patients 3, 4 and 7 were normal so far as the circulatory system was concerned. Patients 3 and 7 suffered from dyspepsia of functional character. Patient 4 had no complaints, but voluntarily subjected himself to the observations.

*Decompensation without Edema*—Patients 1, 2, 5 and 6 showed moderate degrees of cardiac decompensation, due, in patients 1, 2 and 5, to arteriosclerotic heart disease, and, in patient 6, to a rheumatic lesion of the mitral valve. These four patients showed no frank pitting edema, but had definite signs of chronic passive congestion.

*Decompensation with Edema*—Patients 8, 10, 11 and 12 were markedly decompensated with definite pitting edema of the extremities and lower part of the back, and ascites. Auricular fibrillation, established by clinical signs and electrocardiographic examination, existed in patients 8, 10 and 12. Patients 8, 10 and 11 suffered from arteriosclerotic heart disease, and patient 12 from mitral stenosis of rheumatic origin.

*Cirrhosis with Edema*—One patient (no. 9) had portal cirrhosis with ascites and pitting edema of the legs and back.

The patients of all groups were placed at absolute rest in bed for the duration of the observations. They were given salt-free and purine-free diets, and a constant daily fluid intake of 1,200 cc. Daily twenty-four hour specimens of urine were collected and daily specimens of blood secured before breakfast. The specimens were analyzed promptly after collection.

The control periods extended for varying periods of time, averaging six days before the administration of digitalis, with a range of from two to ten days. A short control period occurred only in patient 8, who was badly decompensated, and required the earlier use of digitalis. The control periods of the other patients were extended until the output of urine and the metabolites in the blood and urine remained at constant levels for three days.

The digitalis was given in the form of standardized powdered leaf in weighed capsules. The dose varied with the individual, administration was continued until signs of minor toxicity (usually loss of appetite and nausea, or vomiting) occurred. The doses ranged between 0.7 and 2 Gm. with an average of 1.2 Gm. for the group who showed no diuresis, and 1.4 Gm. for the group who showed diuresis. As has been frequently observed, the susceptibility of the patient to the same standardized digitalis leaf showed considerable individual variation. The edematous patients with cardiac disorders were able to take more of the digitalis without minor toxic symptoms than were the normal subjects, who proved to be the most susceptible group.

The chlorides of the blood were estimated by the method of Austin and Van Slyke,<sup>12</sup> those of the urine by the Seelman-Volhard method,<sup>13</sup> the blood sugar by the method of Somogyi,<sup>14</sup> and the uric acid of the blood and urine by the method of Morris and Macleod.<sup>15</sup>

## RESULTS

The per cent of changes for individual patients are presented in chart 1. The cross hatched blocks represent the maximum daily per cent of changes, i. e., the greatest daily variations found as compared with the controls. The solid blocks represent the average changes observed during the six days following the administration of digitalis as compared with the six-day controls preceding the digitalis, these data are referred to as the total per cent of changes. In considering the changes in the output of urine, and in the various metabolites, the total per cent of changes are more significant than the maximum per cent, the latter indicate the greatest changes that were obtained. The maximum per cent of changes are presented for general interest, and since they were in the same general direction as the average changes, the discussion will be largely according to the average or total changes which are more conservative.

12 Austin, J. H., and Van Slyke, D. D. *J. Biol. Chem.* **41** 345, 1920.

13 Seelman, J. J. *J. Lab. & Clin. Med.* **1** 444, 1916.

14 Somogyi, M. *J. Biol. Chem.* **83** 157, 1929, *Proc. Soc. Exper. Biol. & Med.* **26** 353, 1929.

15 Morris, J. L., and Macleod, A. G. *J. Biol. Chem.* **50** 55, 1922.



As it was quite clear that definite groups of the patients showed diuretic action and others did not, chart 2 was prepared to illustrate correlations between the changes in the output of urine and in metabolites according to diuretic action or its absence in all twelve patients, regardless of condition. The solid blocks represent average changes in those patients showing increased diuresis, and the crossed block, average changes in those who did not. These correlations will be alluded to in

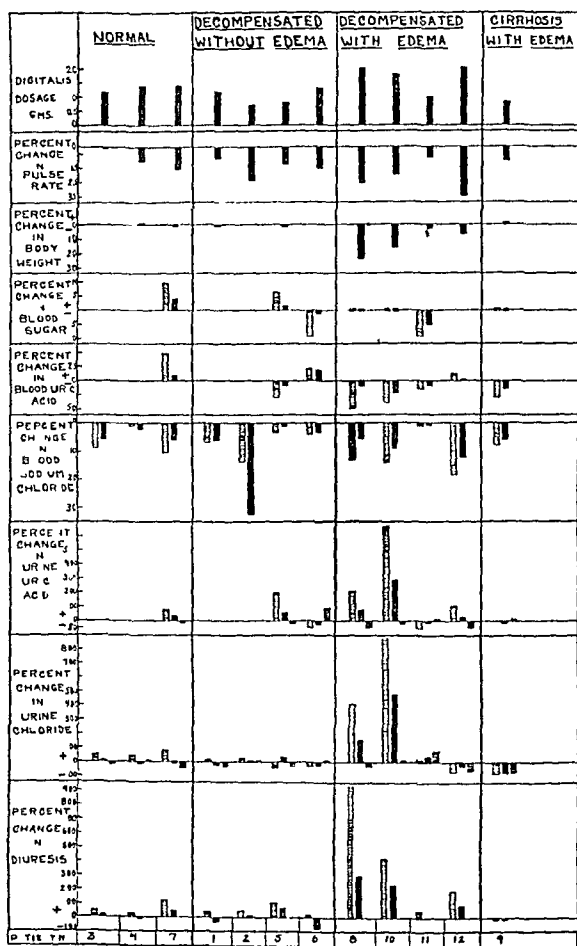


Chart 1—Per cent of changes in diuresis, blood and urinary metabolites, body weight and pulse rate after digitalis in normal and edematous subjects. The solid blocks in the figure, except as to dosage of digitalis, represent average total per cent of changes, the crossed hatched blocks, maximum daily per cent of changes, and the small squared blocks, average per cent of changes in concentration. The solid blocks in the sector on dosage represent total dosage of digitalis.

the text along with the average changes. Unless otherwise indicated, the per cent of changes discussed in the text refer to those of chart 1.

**Diuresis**—The diuresis was variable in both normal and edematous subjects. It usually began on the second day after the digitalis was given (range from one to three days) and persisted during an average

of four days. In patient 8, the diuresis persisted for seven days. In the group of normal subjects, only one (patient 7) showed a diuretic action, namely, a total increase of 52.8 per cent. Patient 3 exhibited a total increase of only 3.8 per cent, and patient 4 showed a total decrease of 4.1 per cent in the output of urine.

Of the four decompensated patients without edema, two (nos. 2 and 5) showed slight increases, and two (nos. 1 and 6) showed decreases in total output of urine. The changes in total diuresis ranged between +70.6 per cent and -15.7 per cent, with an average of -26.9 per cent.

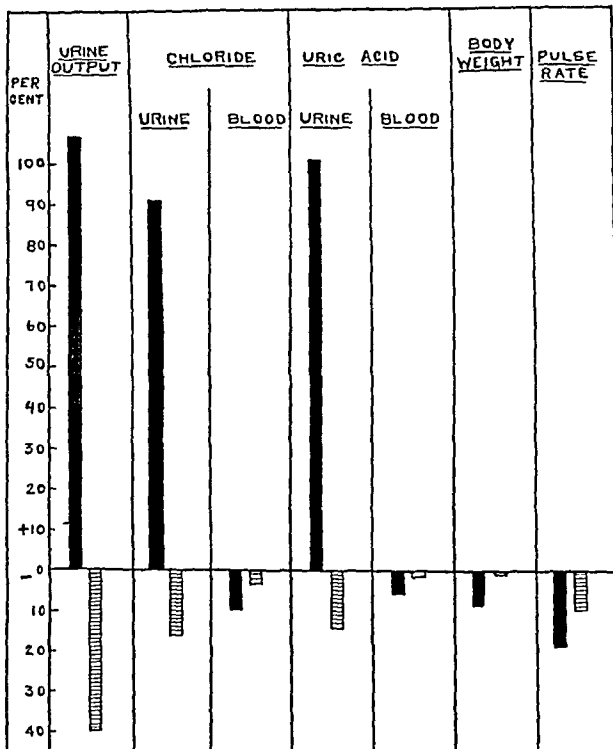


Chart 2—Correlation of per cent of changes in urine output, blood and urinary metabolites, body weight and pulse rate according to presence or absence of diuretic action after digitalis. The solid blocks represent average total per cent of changes in patients showing marked diuresis and the crossed blocks, average changes in those in whom marked diuresis was not present.

As might be expected, the most active diuresis occurred in the group of edematous patients with cardiac disorders. The total diuresis ranged between 0 and 293.3 per cent, with an average of 154.9 per cent. In patient 8, the urine showed a maximum increase on one day of 923.3 per cent, actually, the diuresis removed over 11.5 liters of fluid during the seven day period. One of the definitely decompensated patients (no. 4) showed no change whatever in total diuresis, although his cardiovascular function was markedly improved by digitalis medication.

Patient 9 with portal cirrhosis and edema, showed a diminution in total output of urine namely, — 13.2 per cent. During the period of observation his edema definitely increased.

*Body Weight*—From chart 1 it is obvious that only the group of decompensated patients with edema showed a marked loss of body weight. This loss was greatest for patient 8, who also showed the most active diuresis; this patient lost 23.7 per cent of his body weight, or 34.5 Kg (75.9 pounds) in seven days. Chart 2 illustrates the differences in loss of body weight of subjects with and without diuresis, the former showed a much greater loss of weight.

*Chlorides*—The twenty-four hour output of chlorides in the urine varied directly as the diuresis. The greatest total increases were observed in patients 8 and 10, namely, 156.2 and 473.9 per cent, respectively. Only patient 12 showed diuresis with a decrease of urinary chloride. When diuresis failed to occur, or when the urine decreased in amount, the urinary chlorides were invariably decreased (chart 2). With the increase in twenty-four hour excretion of chlorides, there was sometimes an increase in the concentration of chloride in the urine (patients 10 and 11).

The blood chlorides showed a decrease in all patients. In general, the fall in blood chlorides was greater for the patients who showed diuresis. However, the greatest decrease (— 32 per cent) was found in patient 2, who did not show diuresis. The group of patients who showed diuresis exhibited an average total decrease of 10 per cent in blood chlorides. The group who showed no diuresis exhibited an average total decrease of only 3.5 per cent.

*Uric Acid*—The uric acid of the urine and blood behaved similarly to the chlorides. When diuresis occurred, much greater quantities of uric acid were excreted in the urine (chart 2). This appeared to be purely a washing-out effect, since the concentration of uric acid in the urine was always decreased.

In all patients, except patient 7, the uric acid in the blood fell concurrently with the diuresis and the increased excretion of uric acid in the urine. In patient 7, there was an increase of 10 per cent in the uric acid in the blood in spite of a 20 per cent increase in total uric acid in the urine.

*Blood Sugar*—No constant changes in blood sugar were demonstrable. The changes that did occur were small, did not seem to be affected by diuresis, and probably represented the range of experimental error or natural variations.

*Pulse Rate*—Definite slowing of the pulse occurred in all subjects except patient 3 who was normal. The other two normal subjects (nos 4 and 7) showed slowing of 10.5 and 15.8 per cent respectively. The

greatest slowing (35 per cent) occurred in patient 12, whose heart was fibrillating. The other two patients with auricular fibrillation (nos 8 and 10) also showed marked slowing of the pulse rate. Hence, the typical cardiac slowing of digitalis occurred in patients with normal and abnormal circulatory functions. The degree of cardiac slowing was less in those patients not showing diuresis (chart 2), but this difference might not be as marked in a larger number of patients. The greater slowing of those showing diuresis was related to circulatory abnormality of one sort or another.

#### CONCLUSIONS

1 The diuretic action of digitalis is variable and practically limited to patients with edema of cardiac origin. The diuretic action in human subjects is accompanied by increases in the chloride and uric acid of the urine, and simultaneous decreases in the chloride and uric acid of the blood. In patients not showing increased diuresis, the metabolites of the blood and urine are unchanged or decreased.

Accordingly, the changes in these metabolites of the blood and urine following digitalis medication are mediated differently from those of the metallic and purine types of diuretics, there is a washing-out effect in the kidneys as the result of improvement in the general circulation, which increases renal filtration.

2 On the other hand, the diuresis of metallic and purine diuretics is characterized by simultaneous increases in the chlorides of the blood and urine, an action which is mediated, in part at least, by a direct tissue action of these diuretics and results in a mobilization of the chlorides of the tissues. The effect on metabolites in normal and edematous subjects is the same. This conclusion is based on previously published results.<sup>5</sup>

# EXPERIMENTAL EDEMA PRODUCED BY PLASMA PROTEIN DEPLETION

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According to the conception advanced by Starling,<sup>1</sup> edema may be produced in at least two ways. The blood's capillary pressure (filtration force) may be increased while the plasma colloid osmotic pressure is kept constant, or the plasma colloid osmotic pressure may be lowered while the capillary pressure is kept constant. The rôle played by each of these two factors in fluid distribution has been the object of much investigation. The problem was first approached in our laboratory from the point of view of the capillary pressure change. It was found that acute rises in the arterial pressure (and hence in the capillary pressure) of cats and dogs were accompanied by increased concentration of their blood, the transudate being recovered in the tissues by analyses for water content.<sup>2</sup> Furthermore, direct measurements, in other laboratories, of capillary blood pressure and colloid osmotic pressure in human subjects have given quantitative meaning to the ideas of Starling, for it has been found that the average pressure in the capillaries of the human skin corresponds quite well with the osmotic pressure exerted by the plasma proteins.<sup>3</sup>

The application of the Starling conception of tissue fluid exchanges to explain the edema of nephrosis<sup>4</sup> attracted the interest of clinicians to the second factor mentioned, namely, the rôle played by the osmotic pressure of the plasma colloids in fluid distribution. Analyses performed on the blood of nephrotic<sup>5</sup> and undernourished<sup>6</sup> patients

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From the Departments of Physiology and Pediatrics, School of Medicine and Dentistry, the University of Rochester

1 Starling, E H. *J Physiol* **19** 312, 1896

2 Adolph, E F, and Lepore, M J. *Proc Soc Exper Biol & Med* **28** 963, 1931

3 Landis, E M. *Heart* **15** 209, 1930

4 Epstein, A A. *Am J M Sc* **154** 638, 1917

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revealed consistently that the presence of edema was correlated with low plasma colloid osmotic pressures and low plasma protein concentrations

At the same time the concentration of the plasma proteins was modified in mammals by experimental means. It was observed that edema developed in rats that were fed a diet low in protein.<sup>7</sup> The appearance of edema in such animals was found by later workers<sup>8</sup> to be directly related to the presence of low serum protein concentrations. The method of plasmapheresis<sup>9</sup> was utilized for reducing the plasma protein concentration of dogs, and the edema that resulted was concurrent with the development of low serum protein concentrations.<sup>10</sup> Both low serum protein concentrations and edema were also demonstrated in dogs that had been fed a diet low in protein.<sup>10c</sup>

Edema due to low serum protein concentrations has, therefore, been observed clinically and experimentally in a variety of conditions. Though the cause for the low serum protein concentration may differ, the end-result is the same—massive edema.

It is obvious that if no fluid were available for filtration, edema could not develop, even though the plasma proteins were below the so-called critical concentration. Experimental proof for this belief is contained in the protocols reported by some of the earlier workers who performed plasmapheresis, but who were not primarily interested in producing edema. Most of this literature<sup>11</sup> was found to be unsuitable for analysis from the point of view of the occurrence of edema, because of incomplete data, but some information was gleaned from the protocols of Keri, Hurwitz and Whipple,<sup>12</sup> for in these experiments, in which body weight was used as an index, the absence of edema in hypoproteimic dogs was definitely associated with an inadequate intake of salt and water. Conversely, the occurrence of edema in these hypoproteimic dogs was, as far as could be ascertained, associated with the infusion of considerable quantities of fluid and salt. In the experiments

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11 (a) Abel, Rowntree and Turner (footnote 9). (b) Turner, B. B., Marshall, E. K., Jr., and Lamson, P. D. *J. Pharmacol. & Exper. Therap.* **7** 129, 1915. (c) Morawitz, P. *Beitr. z. chem. Phys. u. Path.* **7** 153, 1906.

12 Kerr, W. J., Hurwitz, S. H., and Whipple, G. H. *Am. J. Physiol.* **47** 356, 1918.

of other investigators,<sup>10a b</sup> sodium chloride solution was supplied by stomach tube to the animals (a procedure not followed by the earliest workers in this field), and in this way a copious supply of salt and water for the development of the edema was insured, and the possibility remains that this supply of salt and water was chiefly responsible for the edema observed. The intake of water and food of their animals was not well controlled. The presence of edema was determined by their gross appearance and by an increase in body weight alone.

The obviously important rôle played by the intake of fluid and salt in the development of this type of edema suggested that a carefully controlled study of the water and chloride balances of hypoproteimic animals, supplemented by analyses of the chloride and water content of tissues obtained at autopsy, might be productive of interesting information.

TABLE 1—*Diets Used in Experiments*

Substance	Diet A					
	Protein, Gm	Fat, Gm	Carbo- hydrate, Gm	Water, Gm	Chloride, Gm	Total, Gm
Milk	21	25	32	560	0.68	638
Bread	17	1	102	70	1.15	191
Sugar	—	—	49	—	—	49
Totals	38	26	183	630	1.83	878

## Diet B

Same composition as that given, except that total quantity was one half that of Diet A.

## METHOD

Ten dogs were studied. They were fed a diet of known amount and composition (table 1) every twenty-four hours. These animals were kept in metabolism cages, and their daily intake of water and volume of urine were measured. They were weighed every day at approximately the same hour. Following a control period of from one to two weeks, they were subjected to plasma protein depletion by plasmapheresis.

Bleeding was performed without anesthesia, either from the femoral arteries or the jugular veins. The blood was drawn into a flask containing approximately 30 cc of 3 per cent sodium citrate solution. From this blood the plasma was removed after centrifugation, and the cells were washed with isotonic sodium chloride solution and centrifugated. This process was repeated again, and finally, the cells, resuspended in calcium-free Locke's solution, were infused into the animal. Samples of arterial blood were removed and placed in bottles containing 0.02 Gm of dried sodium oxalate for analysis. These specimens were taken immediately before the animal was bled and about ten minutes after the plasmapheresis was over. Sterile technic was employed in all but the first animal of this series.

The following analyses of the blood were performed during the control and experimental periods: plasma protein fractionation,<sup>13</sup> determination of the plasma

chloride,<sup>14</sup> hematocrit, determined on oxalated blood that had been placed in a capillary tube and centrifugated for ten minutes at the rate of 1,500 revolutions per minute, and the determination of nonprotein nitrogen.<sup>15</sup> Urinalysis on a twenty-four hour specimen included determinations of the volume, specific gravity, chloride<sup>14</sup> and total nitrogen,<sup>15</sup> and routine examinations for casts, albumin, etc.

At suitable points, the animals were killed by carbon monoxide gas, autopsy was immediately performed, and the tissues removed for sectioning and analyses of the water content and chloride. The water content of the tissues was determined in duplicate by drying previously weighed samples in an oven at from 90 to 100 C until their weight checked within 0.2 per cent. Tissue chloride analyses were done, some in duplicate, on other weighed samples of moist tissue by the method of Van Slyke.<sup>14</sup>

#### EXPERIMENTS

In order to have some standard for comparing the water and chloride contents of the tissues of the experimental animals, it was thought best to establish control values from analyses of the tissues of control dogs which had been killed and on which autopsy had been performed, in the same manner as they had been established in hypoproteimic dogs. Hence one dog (357) that had been kept on the diet listed for three weeks and one (278) that had been taken directly from stock were killed, and their tissues analyzed and sectioned. Autopsy was also performed on a third dog (339) that had been subjected as a control measure to three bleedings and transfusions with defibrinated whole blood, and this animal was also included in this group. Table 2 contains the data obtained from the analyses on the three control animals.

The values obtained for the water content of the tissues agree quite closely with those of Engels<sup>16</sup> as can be seen from table 3. A significant difference was found in these experiments between the water content of muscle from the limbs and that of muscle from the trunk. A higher average value for the water content of muscle of the limb was found than that reported by Engels. But the dogs used by Engels had probably been somewhat dehydrated, for they had been kept without food and water for four days before being killed.

The values for tissue chloride are also in good agreement with those reported by Damiens<sup>17</sup> and Cameron and Walton.<sup>18</sup> The percentage weights of the various organs and tissues were taken from the work of Sato<sup>19</sup> and Stewart.<sup>20</sup>

14 Van Slyke, D. D. *J. Biol. Chem.* **58** 523, 1923.

15 Folin, O., and Denis, W. *J. Biol. Chem.* **26** 473 and 491, 1916.

16 Engels, W. *Arch. f. exper. Path. u. Pharmacol.* **51** 346, 1904.

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20 Stewart, G. N. *Am. J. Physiol.* **58** 45, 1921.



TABLE 2—*Analyses of Tissues of Control Dogs*

Tissue	Dog 357*		Dog 278†		Dog 339‡		Average Chloride Content, Milli mols per 1,000 Gm Tissue
	Per Cent Water Content	Chloride, Milli mols per 1,000 Gm Tissue	Per Cent Water Content	Chloride, Milli mols per 1,000 Gm Tissue	Per Cent Water Content	Chloride, Milli mols per 1,000 Gm Tissue	
Adrenal	61.80	33.5	63.10	27.5	66.35	23.1	63.75
Intestine	74.00	34.6	77.10	33.7	76.00	29.6	75.70
Kidneys	81.23	73.0	78.25	59.3	78.05	62.7	79.16
Liver	75.85	40.3	72.45	45.5	74.50	40.0	74.60
Lung	77.00	60.0	76.25	56.5	78.20	54.3	77.15
Pancreas	72.30	34.3	71.80	38.4	72.55	37.6	72.05
Spleen	77.70	40.9	76.80	39.8	77.75	41.3	77.42
Muscle							
Right fore leg	76.25	16.7	75.70	14.9	76.85	20.5	76.27
Left fore leg	76.80	16.6	76.35	15.5	77.00	19.1	76.71
Chest	72.80	12.8	71.30	13.9	73.15		72.50
Abdomen	74.35	16.5	70.10	15.1	72.85		72.40
Neck	73.85	15.4					73.85
Right upper hind leg	73.30	12.7	75.60	13.5		13.7	75.78
Left upper hind leg	75.30	11.6	75.35	10.6	76.80	16.6	75.50
Right lower hind leg	75.00	10.9	74.25	14.9	77.60	13.6	75.62
Left lower hind leg	76.20	14.1	73.10	12.3	77.30	19.9	75.53
Skin							
Right fore leg	62.45	51.2	59.95	63.9	60.10	67.5	63.83
Left fore leg	64.00	55.2	64.85	65.3	67.85	67.9	65.57
Abdomen	56.60	43.7	53.50	39.6	61.25	45.3	57.12
Neck	48.40	32.3					
Chest	57.20	42.7	41.30	41.1	60.00	56.4	52.80
Right upper hind leg	60.35	43.2	53.75	40.7	58.25	63.7	57.65
Left upper hind leg	51.45	41.2	44.00	39.7	65.95	63.5	53.80
Right lower hind leg	62.15	53.3	59.25	57.0	66.40	61.5	62.57
Left lower hind leg	51.10	54.0	50.20	58.0	67.10	62.5	56.10

\* Dog 357 was kept on diet A for three weeks

† Dog 278 was kept on diet A for three weeks, and subjected to three bleedings followed by infusions of whole defibrinated blood

‡ Dog 339 was taken from stock and immediately killed

TABLE 3—*Average Values for Tissue Chloride and Water Content*

Tissue	Per Cent Water Content		Chloride Content, Millimols per 1,000 Gm Tissue			Per Cent Weight of Tissue Stewart and Sato
	Engels	Author	Damiens	Cameron and Walton	Author	
Adrenal		63.75	52.20	35.00	28.03	0.0121
Intestine	75.40	75.70		37.20	32.63	6.50
Kidney	76.72	79.16	63.10	70.70	65.00	0.57
Liver	73.70	74.60	33.00	38.40	41.90	2.90
Lung	78.70	77.15	67.50	64.80	56.90	0.83
Pancreas		72.05		38.80	36.80	0.22
Spleen	78.60	77.42	50.40	48.20	40.70	0.28
Muscle						
A (Limb)	73.50	75.90	20.30	18.90	14.93	42.84
B (Trunk)		72.92			14.58	
Skin	58.90	53.70			53.30	16.11

The protocols of the most significant experiments are shown. Each of these protocols, although similar to the others in its major features, contains details that are important enough to justify their presentation in full.

#### PROTOCOLS OF EXPERIMENTS

**PROTOCOL 1 (dog 133, female pointer)**—Four hundred cubic centimeters of this dog's blood was deprived of plasma every other day for forty-six days. Diet A was fed. At no time was an increase in body weight recorded. On the contrary, there was a gradual loss in body weight, while the serum protein level was kept quite constantly between 5 and 5.5 per cent despite the plasmaphereses (fig. 1). This might indicate that the animal replaced its serum protein at the expense of its body protein.

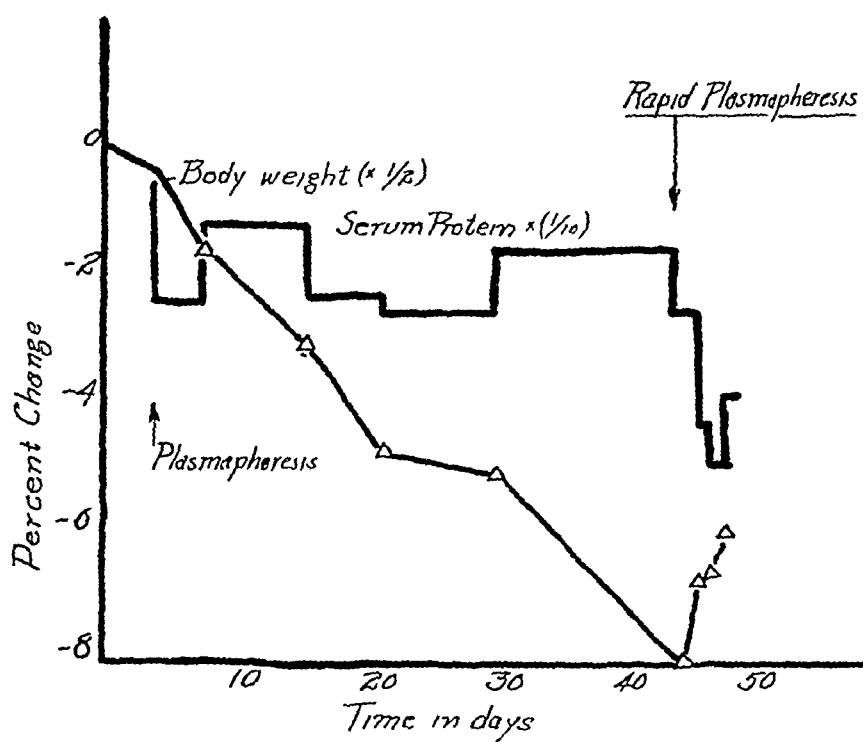


Fig. 1 (dog 133)—Changes in the serum protein and body weight

TABLE 4—Changes in the Serum Protein and Body Weight of Dog 133

Date	Body Weight, Kg	Serum Proteins, Gm per 100 Cc	Albumin, Gm per 100 Cc	Globulin, Gm per 100 Cc	Albumin Globulin Ratio	Water Intake, Cc	Cc of Blood Subjected to Plasma pheresis
3/7	19.20	7.23				1,046	
3/11	19.07	5.53	3.48	2.05	1.70	991	
3/15	18.55	6.37	4.08	2.29	1.76	1,077	
3/30	18.04	5.56	3.32	2.24	1.48	1,360	
4/3	17.40	5.35	3.42	1.93	1.77	895	
4/12	17.28	6.10	3.86	2.24	1.72	710	
4/27	16.04	5.40				880	
4/28	16.77	4.35	2.60	1.75	1.48	1,270	400
		3.94	2.36	1.58	1.50		400
4/29	16.71	4.40	2.46	1.94	1.27	1,160	400
		3.02	1.62	1.40	1.40		250
4/30	17.00	4.47	2.57	1.90	1.35	1,220	350

Beginning on the forty-seventh day, rapid plasmapheresis was performed, as indicated in table 4. Edema appeared when the serum proteins had fallen to an average level of 4.19 per cent. The appearance of the edema was associated with an increased intake of water. The edema appeared grossly to be confined to the hind legs, which exhibited the pitting typical of this condition when pressure was applied.

Autopsy was performed, and the results of the tissue analyses are contained in table 5. The tissues of the hind legs were not analyzed in this dog, but they appeared to be more highly hydrated than those of the fore legs. However, these analyses accounted for only 30 per cent of the hydration observed by measurements

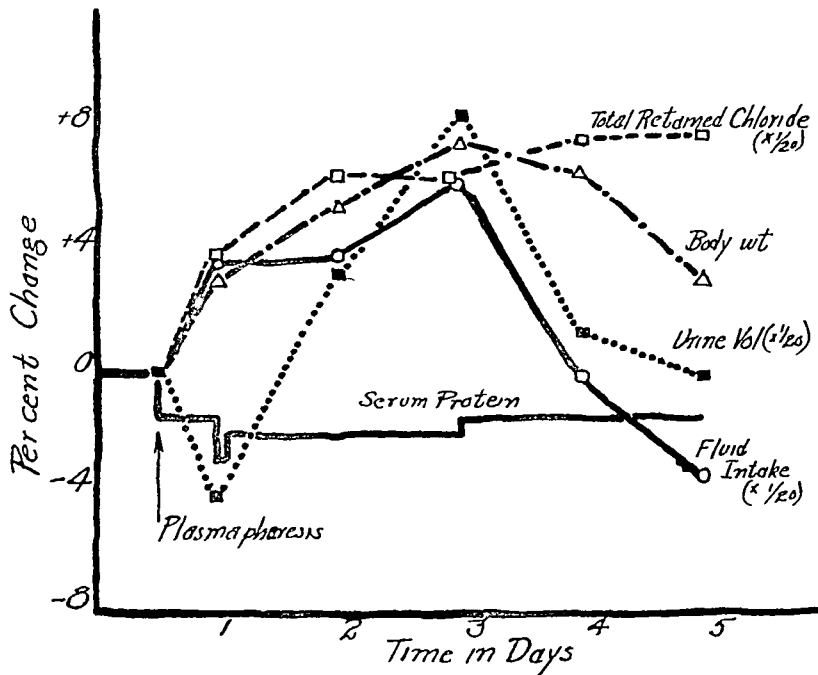


Fig 2 (dog 285) —Water and chloride balance

TABLE 5—Water Content of the Tissues of Dog 133

Tissue		Per Cent Water Content	Excess Water Gm per 1,000 Gm Tissue
Liver		79.70	51.0
Kidneys		83.85	46.9
Spleen		79.30	18.8
Muscle			
Left fore leg		77.85	19.5
Right fore leg		77.25	13.5
Abdomen		77.55	46.3
Chest		75.30	29.8

or weight. For this reason it was thought advisable on later dogs to perform complete analyses of tissues, including the skin and the muscles of the hind legs.

PROTOCOL 2 (dog 285, male setter) —Plasmapheresis was performed as indicated in table 6, aseptic precautions being employed. Edema appeared after the first day of plasmapheresis with the serum proteins at a level of 4 per cent. The development of the edema was associated with a retention of chloride (stored isotonicall

at the start) and an increased intake of water The partial disappearance of the edema was associated with a rise in the serum proteins to 48 per cent, and a great decrease in the intake of water and an increased output of urinary chloride (fig 2 and table 7)

It can be seen from the urinary specific gravity that the urine of the dog in the edematous state was more dilute than his control urine This may have been due to the fact that the lowered colloid osmotic pressure of the plasma prevented

TABLE 6—Blood Changes of Dog 285

Day	Serum Pro tein, Gm per 100 Cc	Albu min, Gm per 100 Cc	Globu lin, Gm per 100 Cc	Albumin Globulin Ratio	Fibrino gen, Gm per 100 Cc	Hemato crit	Plasma Chloride, Milli mols per 1,000 Cc	Plasma Non protein Nitrogen, Mg per 100 Cc	Cc of Blood Subjected to Plasma pheresis
Control	7 06	4 60	2 46	1 87	0 24	49 0	103 8	35 8	
1st*	4 53	3 11	1 42	2 19	0 15	31 0	124 2		300 320
2nd	4 98	3 57	1 41	2 53	0 34	35 9		33 4	450
*	3 05	2 28	0 77	2 96	0 19	31 0	124 3		450
3rd	5 06	3 77	1 29	2 92	0 57	38 3	103 8		
*	3 26	2 09	1 17	1 79	0 24	23 5	120 0	26 8	450
4th	4 78	3 03	1 75	1 73	0 43	25 0	112 0	25 0	400
*	3 47	2 03	1 44	1 41	0 28	21 7	120 0	21 7	350
5th	5 09	3 04	2 05	1 48	0 47	21 8			400
*	4 34	2 82	1 52	1 86	0 13		124 3	29 6	250
6th	5 27	3 04	2 23	1 36	0 34	17 0			200
*	3 68	2 42	1 26	1 92	0 30	17 2	120 0		250

\* Analyses made on samples taken ten minutes after last plasmapheresis

TABLE 7—Water and Chloride Metabolism of Dog 285

Day	Water Intake, Cc	Urine Volume, Cc	Body Weight, Kg	Urine, Specific Gravity	Urine Nitro gen, Gm	Urine Chlo ride, Milli mols	Food Chlo ride, Milli mols	Locke's Chlo ride,* Milli mols	Total Chloride, Milli mols	Retained Chlo ride, Milli mols
Con trol	694	360	15 80	1 025	4 3	53 8	51 7		51 70	
1	1,216	50	16 28		1 1	4 3	51 7	30 10	81 80	77 5
2	1,231	500	16 70	1 013	3 5	30 7	51 7	30 10	81 80	51 1
3	1,626	965	17 00	1 014	8 7	70 0	51 7	24 50	76 20	6 2
4	672	470	16 80	1 017	6 6	23 9	29 0	12 15	41 15	17 2
5	200	355	16 20	1 023	5 3	12 8		17 95	17 95	5 1

\* Locke's solution contains a higher concentration of chloride than does dog plasma The correction for the extra chloride introduced into the dog by this means was made by multiplying the difference between the plasma chloride level before and after plasmapheresis by the estimated plasma volume

absorption of water from the kidney tubules at as rapid a rate as in the normal animal It is also conceivable that filtration of saline through the glomerulus was increased because of the inability of the plasma to retain the fluid supplied to it

The results of the tissue analyses shown in table 8 demonstrate that the retention of chloride indicated by the urinalyses was substantiated by the recovery of the stored chloride in the tissues It is also apparent from these tissue analyses that the edema was widely distributed and prevailed in visceral organs as well as in skin and muscle

TABLE 8—Content of Tissue Chloride and Water of Dog 285

Tissue	Per Cent Water Content	Chloride Content, Millimols per 1,000 Gm Tissue	Excess Water, Cc per 1,000 Gm Tissue	Excess Chloride, Millimols per 1,000 Gm Tissue	Molarity of Stored Chloride
Adrenal	76.70	38.40	129.5	+10.37	0.125
Intestine	81.75	47.00	60.5	+14.37	0.422
Kidneys	79.20	47.90		-17.10	
Liver	73.90	38.10		-3.80	
Lung	80.45	39.60	33.0	+2.70	0.122
Pancreas	78.40	44.70	63.5	+7.90	0.124
Spleen	78.70	29.50		-11.20	
Muscle					
Right fore leg	77.70	21.80	18.0	+6.87	0.382
Left fore leg	76.80	23.00	9.0	+8.07	0.897
Right upper fore leg	74.60	21.90	16.8	+7.32	0.436
Left upper fore leg	76.90	19.80	39.8	+5.22	0.131
Chest	75.40	19.60	4.8	+5.02	0.105
Right upper hind leg	77.30	24.90	14.0	+9.97	0.712
Left upper hind leg	77.95	23.20	20.5	+8.27	0.248
Right lower hind leg	77.60	23.40	17.0	+8.47	0.201
Left lower hind leg	78.10	23.80	22.0	+8.87	0.248
Skin					
Fore leg	69.00	54.60	108.0	+16.20	0.150
Chest	69.85	55.60	111.5	+2.30	0.021
Abdomen	66.55	54.20	78.5	+0.90	0.012
Upper hind leg	71.70	79.30	130.0	+26.00	0.200
Lower hind leg	81.30	71.00	226.0	+17.70	0.078

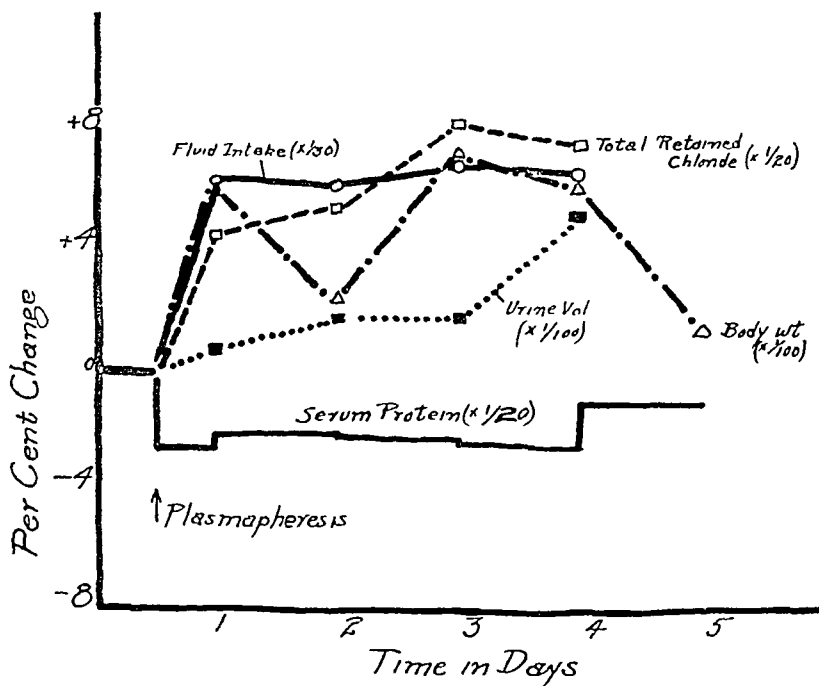


Fig 3 (dog 346) —Water and chloride balance

PROTOCOL 3 (dog 346, male setter) —The data of this experiment are contained in figure 3 and tables 10 and 11. This dog was given in addition to diet B, 1,000 cc of 0.9 per cent sodium chloride solution every day by stomach tube, in order to provide a copious supply of salt and water, and was subjected to plasmapheresis, as indicated in table 11. The total protein levels (table 11) were probably not

TABLE 9—*Distribution and Recovery of Chloride and Water in Tissues of Edematous Dogs*

	Dog 31-2			Dog 285			Dog 286	
	Muscle	Skin	Or gans	Muscle	Skin	Or gans	Muscle	Skin
Chloride recovered (millimols)	79 90	17 60	7 40	51 20	32 56	13 98	45 99	38 30
Water recovered (Gm )	95 70	228 00	20 90	122 00	334 00	6 76	63 50	196 50
Concentration of chloride recovered (millimols)	0 953	0 167		0 384	0 092		0 558	0 142
Per cent chloride recovered	76 10	16 70	7 05	52 30	33 30	14 30	54 60	45 40
Per cent water recovered	30 80	62 40	6 80	30 50	67 20	2 35	30 80	69 20
Total chloride recovered (millimols)	104 90			97 74			84 29	
Total chloride retained (millimols)	142 80			157 22			88 30	
Per cent total retained chloride recovered	73 50			62 00			95 50	
Total water recovered (Gm )	323 70			456 03			260 00	
Total water retained (Gm )	940 00			400 00			238 00	

TABLE 10—*Water and Chloride Metabolism*

Dog 346										
Day	Water Intake, Ce	Urine Volume, Ce	Body Weight, Kg	Urine Specific Gravity	Urine Nitro gen, Gm	Urine Chlo ride, Milli mols	Ingested Chlo ride, Milli mols	Locke's Chlo ride, Milli mols	Total Chlo ride, Milli mols	Retained Chlo ride, Milli mols
Control	465	335	10 98	1 022	5 2	28 2	25 7		25 7	
1st	1,355	600	11 64	1 016	2 5	102 5	179 5	145 0	194 0	91 5
2nd	1,375	950	11 25	1 020	3 3	175 7	179 5	137 0	193 2	17 5
3rd	1,465	925	11 79	1 014	4 6	143 5	179 5	181 5	197 7	54 2
4th	1,350	2,050	11 55	1 010	4 6	304 2	162 5	171 0	179 6	—124 6
5th			11 14							
Dog 31-2										
Control	741	300	11 00	1 025		49 6	51 3		51 3	1 7
1st	4,200	3,200	11 94	1 010		497 0	621 0	17 1	638 1	141 1
Dog 286										
Control	700	300	14 41	1 024	6 1	52 4	51 3		51 3	
1st	2,630	1,435	14 33	1 025	5 7	188 0	205 8		205 8	17 8
2nd	2,460	1,100		1 020	4 7	142 0	205 8		205 8	63 8
3rd	2,455	1,335	15 10	1 014	7 3	184 5	205 8		205 8	21 3
4th	2,430	1,380	14 35	1 011	5 2	210 0	205 8		205 8	—4 2
5th	2,230	1,220	14 51	1 015	5 2	188 0	205 8		205 8	17 8
6th	3,080	2,000	15 00	1 008		304 0	321 8		321 8	17 8
7th	2,430	1,630	14 65	1 012		251 8	205 8		205 8	—46 0

TABLE 11—*Changes in the Blood*

Day	Serum Pro tein, Gm per 100 Cc	Albumin, Gm per 100 Cc	Globu lin, Gm per 100 Cc	Albumin Globulin Ratio	Fibrino gen, Gm per 100 Cc	Hemato crit	Plasma Chloride, Milli mols per 1,000 Cc	Plasma Non protein Nitro- gen, Mg per 100 Cc	Cc of Blood Sub jected to Plasma pheresis
Dog 346									
Control	7 34				0 50	37 7	120 0		200
1st	3 60	2 40	1 20	2 00	0 43	49 3	124 2	31 0	
2nd	4 70	2 59	1 91	1 36		34 3	108 0	24 0	
							124 2		200
3rd	3 88	2 74	1 14	2 40	0 43	19 0			350
4th	3 65	2 45	1 20	2 02	0 65	10 0	128 0		350
5th	3 16	2 45	0 71	3 45	0 86	10 0	124 2		200
6th	5 99	2 99	3 00	1 00	0 54				
Dog 31-2									
Control	6 12	4 13	1 99	2 06		38 0	95 0		275
After plasma pheresis	3 49								275
1st day	4 43	2 72	1 73	1 59		41 2	91 7	38 0	

representative of the true levels for the entire twenty-four hours, for they were obtained from analyses of samples taken immediately after plasmapheresis. From this protocol it is apparent that the edema can be obtained very quickly if enough fluid and salt are made available for storage.

The tissue analyses performed on this dog were made of doubtful value by the fact that shortly before autopsy was performed, the animal was given 2 liters of isotonic sodium chloride solution by stomach tube.

TABLE 12—*Content of Tissue Chloride and Water of Dog 31-2*

Tissue	Per Cent Water Content	Chloride, Content, Millimols per 1,000 Gm Tissue	Excess Water, Cc per 1,000 Gm Tissue	Excess Chloride, Millimols per 1,000 Gm Tissue	Molarity of Stored Chloride
Adrenal	61.90	27.7		- 0.26	
Intestine	78.40	34.3	27.0	+ 1.67	0.062
Kidneys	80.05	69.9	8.9	+ 4.90	0.552
Liver	76.40	46.8	18.0	+ 4.90	0.273
Lung	80.10	70.0	29.5	+13.10	0.444
Pancreas	77.80	40.8	57.5	+ 4.00	0.070
Spleen	78.55	41.5	11.3	+ 0.80	0.071
Muscle					
Right upper fore leg	77.05	28.3	11.5	+13.37	1.160
Left upper fore leg	76.85	24.9	4.5	+ 9.97	2.220
Neck	71.85	27.1		+12.52	
Chest	72.10	32.7		+18.12	
Abdomen	73.90	25.3	9.8	+10.72	1.090
Right upper hind leg	80.40	45.7	45.0	+30.77	0.683
Left upper hind leg	80.40	30.5	45.0	+15.57	0.346
Right lower hind leg	80.50	35.3	46.0	+20.37	0.442
Left lower hind leg	78.10	33.2	22.0	+18.27	0.830
Skin					
Right lower fore leg	70.85	71.6	121.5	+15.60	0.128
Left lower fore leg	68.45	77.3	97.5	+21.20	0.218
Neck	31.15	41.8		- 2.99	
Chest	47.80	48.6		+ 3.81	
Abdomen	56.40	50.4		+ 5.61	
Right upper hind leg	80.65	67.7	219.5	+11.60	0.053
Left upper hind leg	83.00	48.5	243.0	- 7.60	
Right lower hind leg	88.45	55.6	297.5	+ 2.30	0.007
Left lower hind leg	81.40		227.0		

PROTOCOL 4 (*dog 31-2, male collie*) — This dog was subjected to plasmapheresis twice in one day, as indicated in table 11, and was given a total of 3,700 cc of isotonic sodium chloride solution by stomach tube. Three hours after the completion of the plasmaphereses, distinct pitting edema of the hind legs was observed. Six hours after plasmapheresis, a puncture was made through the pendulous skin of the right thigh. Fluid obtained from this site contained 0.3 per cent of protein by Kjeldahl analysis and 115 millimols of chloride per thousand cubic centimeters (0.67 per cent sodium chloride). The albumin-globulin ratio of this fluid was 9.05, indicating that it was mostly albumin. Sixteen hours after plasmapheresis, the animal was killed, and tissues were removed for analysis. There was considerable pleural and peritoneal fluid. The ascitic fluid contained 0.51 per cent of protein by Kjeldahl analysis. Its albumin-globulin ratio was 12.6, and its chloride

content was 116 millimols per thousand cubic centimeters. The plasma chloride value was 917 millimols per thousand cubic centimeters, i. e., lower than the chloride content of the edema fluid, indicating the role of the Donnan equilibrium in the distribution of this ion.

The edema was definitely shown by the tissue analyses (table 12) to be most patent in the limbs and the visceral organs. The upper abdominal, thoracic and neck tissues showed little hydration.

The data from this particular animal are especially decisive in fitting the Starling hypothesis. This is apparently the first instance to be reported in which edema occurred so quickly and in which its appearance was substantiated by tissue analyses. These data also clearly demonstrate the important role played by the intake of fluid and sodium chloride in the development of the edema.

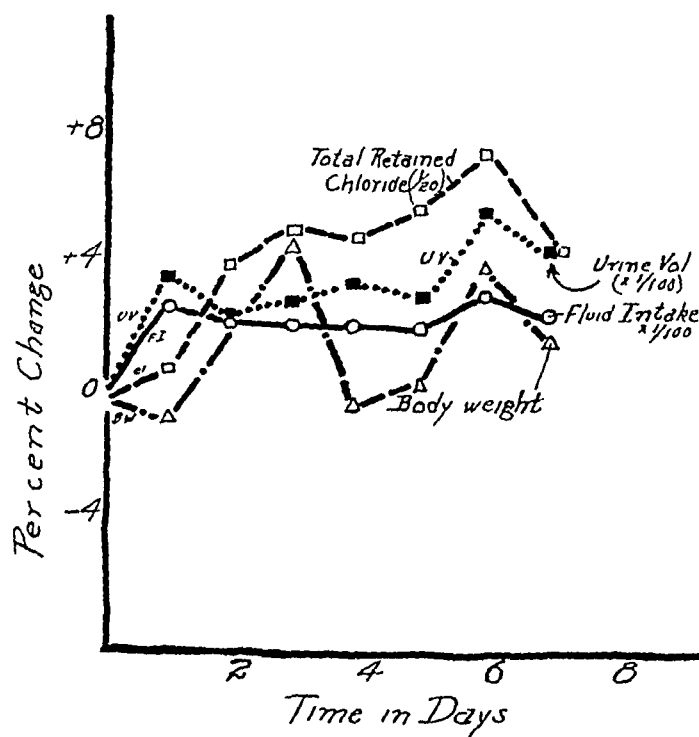


Fig 4 (dog 286) —Water and chloride balance

Given the low plasma colloid osmotic pressure, the speed of development of the edema, therefore, depends on the rapidity with which water and sodium chloride are made available for storage. There is considerable evidence to show that edema may be produced in normal human subjects merely by the ingestion of adequate amounts of isotonic sodium chloride solution<sup>21</sup>. The presence of a low plasma protein concentration would facilitate the appearance of such an edema.

**PROTOCOL 5 (dog 286, male anedale)** —This dog was not subjected to plasmapheresis, and consequently the serum protein level was quite constantly about 7 per cent. It was fed diet A and was also given 1,000 cc of 0.9 per cent sodium chloride solution by stomach tube daily for a period of six days. Although this animal eliminated most of the ingested chloride, it still retained a definite quantity of chloride and water. The chloride and water were recovered by the tissue analyses as shown in table 13.

<sup>21</sup> Baird, M. M., and Haldane, J. B. S. *J. Physiol.* 56:259, 1922.



TABLE 13—*Content of Tissue Chloride and Water of Dog 286*

Tissue	Per Cent Water Content	Chloride, Content, Millimols per 1,000 Gm Tissue	Excess Water, Cc per 1,000 Gm Tissue	Excess Chloride, Millimols per 1,000 Gm Tissue	Molarity of Stored Chloride
Adrenal	65.00	26.4	12.5		
Intestine	77.50	35.6	18.0	+ 2.97	0.165
Kidneys	77.60	53.2			
Liver	73.30	44.5		+ 2.60	
Lung					
Pancreas	72.05	36.3			
Spleen	77.50	40.7			
Muscle					
Right fore leg	78.80	39.6	29.0	+24.67	0.850
Left fore leg	78.00	29.9	21.0	+14.97	0.713
Neck	75.80	23.4	28.8	+ 8.47	0.294
Chest	75.50		25.8		
Abdomen	75.10	26.2	21.8	+11.27	0.517
Right upper hind leg	76.35	17.0	4.5	+ 2.07	0.460
Left upper hind leg	75.60	12.4			
Right lower hind leg	76.40	17.5	5.0	+ 2.57	0.512
Left lower hind leg	75.60	17.0		+ 2.07	
Skin					
Right fore leg	70.80	80.0	121.0	+21.30	0.176
Left fore leg	70.55	78.8	118.5	+20.10	0.170
Neck	69.40	73.4	107.0	+14.70	0.137
Chest	69.50	73.0	108.0	+14.30	0.132
Abdomen	70.65	69.4	119.5	+13.70	0.115
Right upper hind leg	71.95	78.2	132.5	+19.50	0.147
Left upper hind leg	70.60	76.5	119.0	+17.80	0.150
Right lower hind leg	75.85	72.7	171.5	+14.00	0.082
Left lower hind leg	70.00	77.2	113.0	+18.50	0.164

From a consideration of the data from this experiment, it is apparent that there is a definite similarity between the process of salt and water storage in this animal and in the hypoproteimic dogs

#### COMMENT

1 *Total Protein*—Edema occurred in the dogs when the serum protein level was about 4 per cent

2 *Albumin-Globulin Ratio*—It can be seen from protocol 1 that when plasmapheresis was performed over a long period of time comparatively small percentages of the total blood volume of the dogs being bled at one time, the albumin-globulin ratio was lowered. There was no massive albuminuria in this animal that could have accounted for this lowering of the ratio. These data may be taken as evidence for the fact that under the particular conditions stated in this protocol, the globulin fraction is restored faster than the albumin fraction. This confirms the work of Keir, Hurwitz and Whipple<sup>12</sup>

The dogs reported in protocols 2, 3 and 4 were subjected to a type of plasmapheresis that was intermediate between the "rapid" and the "slow" plasmapheresis performed by Whipple and his co-workers<sup>22</sup>. The resultant albumin-globulin ratios were also a mixture of the two types of results reported by these investigators. Whipple and his

<sup>22</sup> Kerr, Hurwitz and Whipple (footnote 12) Smith, H. P., Belt, A. E., and Whipple, G. H. *Am J Physiol* **52**: 54, 1920

co-workers<sup>12</sup> reported a lowering and even a reversal in the albumin-globulin ratio after slow plasmapheresis. It is evident from the protocols on the regeneration of the plasma proteins after rapid depletion<sup>22</sup> that, after moderately great amounts of plasmapheresis, the albumin fraction is restored more quickly than the globulin. It was found in our dogs that, during the first day or so, the albumin fraction was restored more rapidly than the globulin fraction. Later, the globulin fraction was replaced more rapidly.

Albumin-globulin ratios were also determined immediately before and ten minutes after plasmapheresis. It was consistently found by these analyses that the albumin fraction was replaced more rapidly than the globulin. This evidence confirms the observations of a number of workers<sup>24</sup>.

The cause for the early restoration of the albumin fraction is not very clear. It may be that there is a good reserve store of it available. Drinker<sup>23</sup> has presented some evidence on this point. He believes that the emergency restoration of plasma protein immediately after plasmapheresis is made at the expense of the lymph. He finds high albumin-globulin ratios for lymph and believes that the influx of lymph and tissue fluid into the blood is one of the reasons for the rise in the albumin fraction immediately after plasmapheresis.

The objections that can be raised against any method which arbitrarily divides the serum proteins into only two groups should be kept in mind in considering these data on albumin-globulin ratios.

3 *Fibrinogen*—This protein was replaced with extreme rapidity after plasmapheresis, and in many instances tended to reach values decidedly above the control figures, regardless of the fact that the other plasma proteins were at very low levels. A similar reaction of fibrinogen to plasmapheresis was observed by Smith, Belt and Whipple<sup>25</sup>.

4 *Red Corpuscles*—There was a gradual fall in the hematocrit in most of the experiments that were performed. No attempt was made to remedy this by a transfusion of blood from another animal. The reason for the destruction of the red cells (which in dog 285 was accompanied by hemoglobinuria) is not definitely known. However, a good portion of the red cell loss was probably due to hemolysis promoted by an increase in fragility of the cells caused by the mechanical violence to the cells during the process of plasmapheresis.

It may be claimed that the anemia indicated by the low hematocrit values, or the resulting poor oxygen supply to the tissues, was a primary

<sup>23</sup> Loewen, D. F., Field, M. E., and Drinker, C. K. *Am J Physiol* **98** 70, 1931.

<sup>24</sup> Morawitz, P. *Beitr z chem Phys u Path* **7** 153, 1906. Loewen, Field and Drinker (footnote 23).

<sup>25</sup> Smith, Belt and Whipple (footnote 22).

factor in the production of these edemas. However, the recovery of transudates low in protein content and the results of various control procedures would indicate that these factors were not the major ones.

5 *Water in the Tissues*—The data obtained from all of the tissue analyses have been summarized in table 9. The comments cited are based on this table.

The edema has been described on the basis of gross observation as being localized more or less in the hind portion of the animals with little or no involvement of the fore legs.<sup>101</sup> The inadequacy of conclusions drawn in this manner are evident from the analyses of the tissues that were performed. These show that the edema is more widely distributed than has been reported. Appearances to the contrary, the fore legs are overhydrated, although not to as great a degree as the hind legs. It is interesting to observe that although both the muscle of the hind limbs and that of the fore limbs are involved in this edema, the upper abdominal, thoracic and neck muscle usually exhibit normal water contents. Skin, as shown by the analyses, is quite uniformly hydrated all over the body, although the tendency is for it to be slightly more hydrated in the region of the hind legs. The analyses of the visceral organs show that these tissues are considerably hydrated. It is interesting to speculate as to the factors concerned in the distribution of this edema. In the Starling conception, two factors that probably are quite uniform all over the body at any one moment are the tissue colloid osmotic pressure and the plasma colloid osmotic pressure. The factor that may then be considered as the variable is the effective hydrostatic pressure in the capillaries. There are, of course, differences in the absolute capillary pressures in the different regions of the body. However, these differences are not the only ones. One tissue may be unable to expand as much as another because of the binding force exerted by cell membranes or enveloping sheaths, etc. This extra force prevents the tissue from swelling to its fullest extent and thereby eventually opposes the capillary filtration pressure. It is, therefore, suggested that in applying the Starling hypothesis, besides considering the factors of capillary pressure and plasma colloid osmotic pressure and extracapillary colloid osmotic pressure (which is presumed to remain constant throughout one of our experiments), the, at present, unmeasured force of tissue turgor or pressure should be recognized as being of definite importance in this system. "Tissue pressure" has been recognized by Landerer<sup>26</sup> and Krogh<sup>27</sup> as an important element in the maintenance of the water equilibrium of the tissues. The tendency for edema fluid to accumu-

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26 Landerer, A. S. Die Gewebsspannung in ihrem Einfluss auf die örtliche Blut- und Lymphbewegung, Leipzig, J. C. W. Vogel, 1884.

27 Krogh (footnote 5, p. 304).

late in the serous cavities and in "soft" tissues (e g, the eyelids) may be due to the ability of these tissues to increase in volume without changing their tensions appreciably

Differences in the ability of protein to pass out of the blood in the different regions may explain in part the distribution of the edema. However, these differences are probably at a minimum following plasmapheresis, for several mechanisms are present which tend to raise the serum protein level, possibly at the expense of the protein of the tissue fluid

The data from the organ analyses are, so far as can be ascertained, the first to show where edema fluids are deposited. It appears important to us to know definitely that this edema involves visceral organs as well as other tissues. There is pulmonary edema in these animals. The pancreas in all of the edematous dogs ranged from 55 to 10 per cent overhydrated. In the protocols of Whipple, Smith and Belt<sup>25</sup> there were several instances in which pancreatic edema was noted after plasmapheresis, while gross general edema was not noted.

The tissue analyses reported from this investigation do not by any means represent the extremes to which this edema may develop. In fact, the changes reported may be regarded as being only moderate ones which could have been accentuated by prolonging the experimental period.

6 *Tissue Chloride*—The tissue chloride data confirm the data on chloride balance of the dog as a whole by showing that there is a definite chloride storage in all of the analyzed tissues. It can be seen from table 9 that 61 per cent of the recovered chloride was found in muscle where it was stored hypertonically, while 66 per cent of the recovered water was found in the skin. The extra chloride in the skin appeared to be stored isotonicly.

In considering the distribution of water and chloride in the edematous tissues, we should remember that normally the skin has a low water content and a high chloride content. Muscle, on the other hand, has normally a high water content and a low chloride content. It may be that these properties are vitally concerned in deciding which of the tissues shall store more water and which shall store more chloride.

7 *Water and Chloride Metabolism*—All but a negligible amount of the ingested chloride of these animals was sodium chloride. However, how much of the urinary or tissue chloride was accompanied by sodium is not known, but most of the changes found were probably changes in sodium chloride metabolism. The experiments demonstrate that definite retentions of chloride and water are associated with the appearance of the edema. The lowering in the serum protein permits the escape

of water and salt whenever the supply of these materials is adequate. At no time is water stored by these animals without some chloride being simultaneously retained.

If the isotonic sodium chloride solution is not supplied to the dog by stomach tube, the animal retains some chloride and ingested water from the food and Locke's solution, storing the combination isotonicly. Data on the body weight seem to indicate that the retained chloride is stored isotonicly by the body as a whole, but that the chloride is recovered in isotonic proportions in skin and in hypertonic concentrations in muscle.

The abatement of the edema is definitely associated with a rise in the serum proteins and is accompanied by a diuresis, an increased excretion of chloride and a decrease in the intake of fluid. In some cases, the diuresis is a water diuresis, and little of the stored chloride is eliminated. It has been claimed, therefore, that the kidney in this condition cannot eliminate chloride as well as the kidney of a normal dog. However, we have definite evidence for the fact that the chloride excreting power of the edematous animals is quite normal. The dogs of protocols 2, 3 and 4 were given great amounts of chloride, and they succeeded in eliminating amounts of it that were far above the control excretions of chloride. It can be said, therefore, that probably a good portion of the chloride in the edematous dog gets into the tissues before it can be excreted by the kidneys. The fact that chloride does not accompany the water in all instances when diuresis occurs is no proof of damaged kidney excreting power for chloride. It may be that here again, the tissues hold on to the chloride tenaciously so that it is not offered to the kidney for excretion.

Dog 286, as was stated, had been given 1 000 cc of 0.9 per cent sodium chloride solution by stomach tube for a week and had then been killed and autopsy performed. The tissue analyses revealed the fact that this dog was slightly overhydrated and had retained some chloride in its tissues, regardless of the fact that its plasma proteins were at the normal level, for this animal had at no time been subjected to plasmapheresis. Retention and storage of chloride after ingestion of sodium chloride by normal dogs has been reported consistently by Engels<sup>1c</sup> and Wahlgren<sup>28</sup> and others.

The similarity between the results of the tissue analyses of this dog and those of the hypoproteinic ones suggests that low serum protein edema in dogs is a sodium chloride edema that has reached extreme proportions because of the lowered plasma colloid osmotic pressure which facilitates filtration of fluid into the tissues.

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28 Wahlgren, V. *Arch f exper Path u Pharmacol* **61** 97, 1909

Restriction of the fluid and salt of the diet has been advocated for years in the treatment of edema in human patients<sup>29</sup> These experiments justify the employment of such measures in the management of the edemas of nephrosis, malnutrition and other conditions in which low serum protein concentrations occur

#### CONCLUSION

A study was made of the water and chloride metabolism of normal dogs and of dogs that had been rendered hypoproteimic by plasmapheresis The sites of deposition of water and chloride were ascertained by tissue analyses

On the basis of the data obtained, it is concluded that the edema that occurs in dogs rendered hypoproteimic by plasmapheresis is a sodium chloride edema, the development of which can be hastened by increasing the intake of fluid and sodium chloride of these animals

The sound advice and encouragement rendered by Dr E F Adolph and Dr S W Clausen were of inestimable value in the initiation and consummation of these experiments

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<sup>29</sup> Widal, F, and Javal, A J de physiol et de path gen 5 1107 and 1123, 1903

## Book Reviews

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**The Rheumatic Infection in Childhood** By Leonard Findlay, M D, D Sc M R C P, Visiting Physician, East London Hospital for Children, Shadwell, Honorary Member, American Pediatric Society, Honorary Member, Canadian Pediatric Society, Honorary Fellow, Medical Society, Budapest, Honorary Member, Interstate Medical Association, North America, Formerly Professor of Pediatrics, Glasgow University, and Director of Child Welfare, League of the Red Cross Societies, Geneva First edition Cloth Price, \$3.50 Pp 179, with charts and illustrations New York William Wood & Company, 1932

On reading this book one is further impressed with the immense amount of work that has been done in this field. The book consists of a critical analysis of 701 cases of rheumatic infection that have come under the author's observation during the past sixteen years. While the book contains nothing that is essentially new, the facts obtained from the study are well organized and presented and form a definite addition to the existing material. One realizes that the study of even so large a series as 701 cases does not tell the story of rheumatic infection. It tells only the story of rheumatic infection in one locality, studied by one observer or group of observers. Consequently, the opinions formed from the study of this group will not go altogether unchallenged.

In this series of 701 cases there was a total of 489 cases of heart disease. Other authors have found the incidence of heart disease a bit higher. One wonders whether the author's diagnostic criteria would correspond to those generally accepted. He speaks of a purulent effusion about the joints in certain cases. Many observers will not admit that a suppurative arthritis falls within the group generally accepted as acute rheumatic fever.

The author is not convinced that the Aschoff body is the typical lesion of rheumatic heart disease, much less does he favor the notion that this lesion occurs elsewhere as a result of rheumatic infection. He states that he has never had demonstrated to him an Aschoff body in the heart of a child who has been under his observation. He explains the round cell infiltration as the result of disintegration of muscle. He does not state the number of cases that were subjected to histologic study, and there were postmortem studies in only 37 cases, not a great number.

A considerable portion of the book is devoted to a discussion of valve disease, its incidence and prognostic value. An attempt is made to correlate the occurrence of valvular pathologic changes with other features of the disease. He states, for instance, that chorea is much more frequently accompanied by mitral stenosis than is arthritis. In a condition that causes such widespread damage as does rheumatic disease, such correlations are likely to be highly fortuitous even in so large a series as this one. Again, lack of adequate postmortem material might throw some doubt on diagnostic accuracy. The diagnosis of aortic regurgitation based on a diastolic murmur alone, without any of the peripheral vascular phenomena, is a highly hazardous procedure.

The author has little in common with those who admit the occurrence of rheumatic pneumonia. He believes that all the pulmonary findings in connection with rheumatic infection may be satisfactorily explained on some other basis. Nor has he ever seen the Aschoff body or its analogue in the lung. His stand in this matter seems a bit inflexible.

There is an excellent discussion on the "pre-rheumatic state," a term with which the author has little patience. The book is concluded with a sane and conservative discussion of treatment and the necessity for after-care of the child with cardiac disease.

The book constitutes a worth-while addition to the literature on rheumatic infection, but it must not be assumed that all of the opinions expressed will meet with unanimous approval.

**Pathologische Physiologie** By Ludolph Krehl Fourteenth edition Price, 39 60 marks Pp 716 Leipzig F C W Vogel, 1932

This massive book, now in its fourteenth edition, is to be the first of a three volume work on the origin, recognition and treatment of disease of the internal organs of the body. The author, who for many years has been the head of the Medical Clinic of Heidelberg, ranks foremost among the older and greater German internists and teachers. His pupils include a number of men who now head other university clinics, such as Stepp in Breslau and Morawitz in Leipzig, his influence on German medicine through his writing and teaching as well as through his prestige and activity in the principal medical societies of Germany is enormous.

The subject matter of the volume at hand is treated from the standpoint of the physician. With all due regard for the importance of investigation on animals, the process of disease in man is considered to be so extraordinarily complex that in the end observations on the patient are of primary importance. Knowledge gained at the bedside thus receives the foremost consideration, although the laboratory is not seriously neglected. There is much that is well known and some material with which the general reader will be less familiar, but the chief value of the work lies in the wealth of problems and questions to stimulate the investigator to further study. There is little didacticism. In fact, the point of view is so philosophic as to make it doubtful whether it will appeal to the "practical" American mind. This is further accentuated by that peculiar verbosity which few German scientific writers seem able to avoid. The book is decidedly not one for the "man who reads and runs," in fact, the style is so little considerate of the reader's time as to constitute a distinct annoyance. What is said could be compressed at least one-half without the slightest sacrifice of subject matter.

It is impossible in a review to give more than a cursory insight into the mass of material covered. The following topics form the subject matter of the various chapters.

The first section opens with a consideration of constitution in its broadest sense, an obscure subject which is handled in an interesting manner. Infection and immunity are treated somewhat incompletely, at least the more modern conceptions in this field are rather neglected. Fever and metabolism receive adequate consideration with considerable subordination, however, of all but the German literature. It is surprising that throughout the book one finds scarcely any reference to work in England and America. "Auslander" discoveries, with few exceptions, are either neglected entirely or considered only through the writings of German reviewers. The section on the nervous system is delightful, particularly in the exposition of such topics as unconsciousness, automatism and the influence of the will. The chapter on the circulation is tiring because of the exhaustive treatment of much obvious material. In the chapters dealing with blood, digestion, respiration and urination, the treatment each subject receives, although frequently confusing, is refreshing and inspiring. The many questions raised about matters which are still unexplained and the doubts expressed regarding much that one is accustomed to accept as fact must prove stimulating to all thoughtful students of medicine.

**Hépatites et cirrhoses** Classification, pathogénèse et morphogénèse des hépatites diffuses aiguës, subaiguës et chroniques d'après les notions récentes sur la physio-pathologie hépato-biliaire. By Guy Albot, ancien interne des hôpitaux de Paris. Price, 34 francs Pp 248, with 56 figures. Paris Masson & Cie, 1931.

The author of this excellent, well illustrated monograph considers cirrhosis to be the result of various types of hepatitis. The work is primarily anatomic, but the point of view is clinical. The latest histologic methods have been employed in a detailed study of cellular changes noted in the liver under various experimental conditions and also in numerous lesions found at operation or at autopsy in human beings.



Three great groups of diffuse hepatitis are recognized the toxic-infectious type, the hepatitis of biliary stasis and the hepatitis of venous stasis. The first group, to which the author applies the term "cytolytic hepatitis," includes the familiar clinical syndromes of acute catarrhal jaundice, acute, subacute and chronic atrophy of the liver and atrophic cirrhosis, together with other less common forms, such as the cirrhosis of Hanot. The author distinguishes three stages, demonstrable experimentally and also seen in human material. The initial changes are located in the periportal regions and consist of isolated or grouped microchondriolysis and cellular degeneration, accompanied by dilatation of the bile capillaries. In the second stage there is a generalized clarification of all of the cells of the lobule, hypertrophy of the lobule and a proliferation of reticular tissue. The third period is that in which the lesions become asymmetric and are no longer periportal in distribution, but seem to involve the less resistant cells wherever they are located, frequently at the center. If the acute process does not terminate fatally, a cirrhosis develops the extent of which depends on the severity of the hepatic injury and on its duration. As long as the hepatitis continues, the resulting cirrhosis is progressive.

The group due to biliary stasis may be divided into three varieties: those due to pure stasis, those due to stasis and an accompanying cholangitis and those due to stasis and accompanied by a diffuse inflammatory process. These changes are well illustrated. In this group the cirrhosis does not progress after the biliary stasis disappears.

The hepatitis and cirrhosis attributed to venous stasis are not considered in detail.

The preface is written by Professor Roussy, who expresses the opinion that the book will take its place in the literature of diseases of the liver. In the opinion of the reviewer, the work is a significant contribution well worth the careful consideration of those interested in hepatic disease.

**Cytology and Cellular Pathology of the Nervous System** Edited by Wilder Penfield. Vols. 1, 2 and 3. Price, \$30. Pp. 1267. New York: Paul B. Hoeber, Inc., 1932.

The first volume of the system deals with normal and pathologic ganglion cells, nerve fibers, their endings and the nerves of the blood vessels. The second volume treats with mesodermal tissues of the brain, including microglia, meninges, choroid plexus and blood vessels, in another part of this volume are discussed the pineal gland, hypophysis, optic nerve, retina, choroid and papilla. The third volume is largely taken up with tumors, malformations, with which are included tuberous sclerosis, amaurotic family idiocy, Schilder's and Pelizaeus-Merzbacher's diseases and hydrocephalus.

The topics mentioned are only a few of the numerous phases of neuropathology and normal histology of the central and peripheral nervous systems. The most interesting and elaborate contribution is that of del Rio Hortega. It deals with the form of supportive connective brain tissue known as microglia, the cells of which are termed microgliaocytes or Hortega cells. These represent the reticulo-endothelial system of the central nervous system and are analogous to histiocytes or resting wandering cells of Maximow, also known as polyblasts. They are supposed to perform the function commonly assigned to the neuroglia—to transform damaged brain tissue into lipoids and to remove them to the blood vessels. Equally instructive and exhaustive is the contribution of Boeke on nerve endings, with numerous illustrations. Some of the other contributions are covered in a rather elementary manner, and in some too much space is given to the elaboration of the author's personal views, which in many cases are by no means accepted. The nomenclature is occasionally unusual, is not always sufficiently clear by illustrations and, for these reasons, is somewhat confusing. Because of the great number of contributors some shortcomings, of course, were to be expected in a work dealing with highly specialized topics. The system was evidently prepared

with a view to convey an idea of the fundamentals of the modern normal and pathologic histology of the central and peripheral nervous systems. As an acquaintance with such fundamentals is of utmost importance to the neuropathologist or pathologist in general, as well as to the clinical neurologist, the value of the collective treatise is obvious.

**Kolloidreaktionen der Rückenmarkflüssigkeit Technik, Klinik und Theorie** By Dr. Willy Schmitt Price, 13 50 marks Pp 181 Dresden Theodore Steinkopff, 1932

This is a timely book on the subject of colloid reactions of the spinal fluid. It includes theoretical discussions as well as technical and clinical interpretations of data.

The author begins with a discussion of the material used in the colloid test of the spinal fluid, and emphasizes the importance of absolutely clean glassware and the use of standardized substances. There is a detailed technical description of the gold reaction, the Mastix reaction, the paraffin reaction and several other tests. The descriptions are not only set forth in detail, but are compared with the other colloid reactions of the spinal fluid. The author emphasizes the relationship of the individual tests with various pathologic conditions of the brain and spinal cord and mentions the various colloid reactions obtained by the different methods as applied to disease conditions of these organs. There is also a discussion dealing with those technical methods not used as frequently as the Lange test.

The last chapter deals with the theory underlying the various colloid reactions of the spinal fluid, with particular emphasis on the physicochemical changes that occur. There is also a section of the book devoted to the literature on the various methods described in the text and black and white photographs showing the various reactions in the test tubes with the different methods used.

One does not obtain the impression from reading this book that the various tests employed, excepting the Lange, are of great practical service in the diagnosis of disease conditions. From the academic standpoint, they are of interest and will possibly help the clinician in arriving at an understanding of the pathology of the disease. Each test must be studied separately by the clinician.

For those interested in the subject of colloid reactions of the spinal fluid, this book will be of assistance in many ways.

It is gratifying to note that the type in the book is large and the German is relatively simple, which will aid the English-speaking workers who may have need to refer to the book.

**Health Protection for the Preschool Child** By George T. Palmer, Dr. P. N. Mahew Derryberry and Philip Van Ingen, M.D. Price, \$2.50 Pp 275, with 40 tables and 57 charts New York Century Company, 1931

To have been privileged to hear Dr. Philip Van Ingen and Dr. George T. Palmer recite the contents of this volume at the White House Conference still remains as one of the thrills that great Congress provided. The accuracy, the completeness and the sincerity of purpose of this study were made so impressive through the personality of the speakers that one who heard them almost hesitates to invade the impersonal domain of the printed page. There were many, however, who were not present, and to them will this volume stand as monumental evidence of an untiring effort to obtain facts—facts gleaned from one of the most extensive statistical studies ever attempted.

The pediatric world should be impressed, as a result, with its tremendous strength as a strong contender in the field of preventive medicine, while at the same time it should feel chagrined at the evident failure it has made. We have failed to apply extensively those well founded principles of prevention so efficiently demonstrated when used.

Three specific issues have been investigated, namely, routine health examinations of the preschool child, dental examinations and immunization against

diphtheria and smallpox. In none of these places has the 50 per cent mark been passed in any established normal community, while in many specific instances the percentage is appallingly low.

The urge for a more concerted effort by the pediatrician, the general practitioner and the numerous health departments is so evident through the statistical evidence presented that not to recognize it is nigh on to stupidity.

The members of the committees on medical care for children of the White House Conference deserve the highest praise for this most complete and stimulating study so amply presented in this volume.

**Die Zuckerkrankheit und ihre Behandlung im Kindesalter** By Richard Priesel and Richard Wagner, Vienna. Price, 15.60 marks. Pp 211. Leipzig Georg Thieme, 1932.

In this small book, which is really a detailed enlargement of the monograph "Die Pathologie und Therapie der kindlichen Zuckerkrankheit," published by the same authors in 1926, Priesel and Wagner have presented an up-to-date discussion of the pathologic physiology, diagnosis and treatment of diabetes in children.

The book is divided into two parts. The first six chapters deal with the theoretical, clinical and laboratory aspects of diabetes, and the last two chapters with treatment. An extensive bibliography, chiefly of European literature, is included. Although the authors have nothing new to present regarding either the clinical or the laboratory phase of diabetes, their large experience and the practical manner in which they present their method of handling children make this a worthwhile volume.

**50 Jahre Kongress für innere Medizin, 1882-1932** By Georg Klemperer, Berlin. Paper. Price 9.80 marks. Pp 164. Munich J. F. Bergmann, 1932.

If one desires a brief survey of the trend of medical thought in Central Europe during the last forty or fifty years, this booklet will fill the need fairly well. It consists of a sketch of the advances in the various branches of internal medicine as presented at the meetings of the Congress by its leaders in each subdivision from year to year.

For a source of definite information it cannot be recommended, for a historical outline, it is mildly interesting.

## INSULIN DOSAGE AND BLOOD SUGAR CHANGES

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AND

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Immediately following Banting's announcement of a method of preparation that would permit insulin to be obtained in sufficient quantities to make its use in experimental work practicable, and more especially with the availability of commercial preparations of insulin, there has been an avalanche of publications on carbohydrate metabolism. This was natural and to be expected. However, in spite of the multiplicity of papers, our knowledge of the deeper significance of insulin is still disappointingly poor. There seems to be, also, a certain amount of confusion concerning some of the more obvious results of insulin administration. For these reasons it seems desirable to us at this time to present an experimental review of some of the simpler aspects of insulin activity.

In view of the abundant recent and excellent reviews of the literature that have appeared there is no occasion to burden this paper with what at best could be but a repetition.<sup>1</sup>

One gathers from the literature that it is the general opinion that little useful knowledge may be expected from a study of the effects of the injection of small amounts of insulin. One of the reasons for this opinion is that it is thought that any change in the insulin concentration of the blood that might be brought about by such small additions would be compensated for by changes in the rate of discharge of the animal's own carbohydrate-controlling hormones. Just what hormones would be involved undoubtedly would depend on the particular circumstances of the moment. Now, perhaps, there would be an increase in the rate of the discharge of epinephrine, again, there might be a decrease in the pancreatic activity, or yet again it might be that still others of the endocrine system would be involved, i.e., the pituitary or

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<sup>1</sup> Macleod, J. J. R., and Orr, M. D., in *The Biological Standardisation of Insulin*, Geneva, League of Nations Health Organization, 1926, C. H. 398, p. 11.  
Macleod, J. J. R. *Carbohydrate Metabolism and Insulin*, London, Longmans, Green & Company, 1926.  
Staub, H. *Pankreas*, in *Bethe Handbuch der normalen und pathologischen Physiologie mit Berücksichtigung der experimentellen Pharmakologie*, Berlin, Julius Springer, 1930, vol. 16, p. 557.  
Cori, C. F. *Physiol. Rev.* **11** 143, 1931.

the thyroid In addition to this hypothetical difficulty, it is also thought by some that it is not possible to differentiate the small changes in the blood sugar concentration, which might be caused by such small doses, from the spontaneous variations of the initial sugar concentration

It is the primary purpose of this paper to present a study of this particular field, that is, to develop a method, if possible, that will permit the study of the effects of small doses of insulin on the concentration of sugar in the blood, and to make use of the method, when developed, in such a study It is the hope also that the method may be sufficiently sensitive to make possible the study of such spontaneous or physiologic changes in the concentration of blood sugar as may be presumed to be a part of the normal equilibrium of the carbohydrate metabolism Though this is our primary purpose, it has seemed necessary or desirable to stray from it at times Thus, for purposes of comparison, it is necessary to include a study of the effects of somewhat heavier doses A cursory survey of the literature leaves no doubt that much has been learned from studies of the effects of the administration of large amounts of insulin, and it is highly probable that much of interest and importance still awaits investigators in this field It is, however, hardly probable that an animal, during its entire normal life, is ever subjected to insulin changes that are at all commensurate with those imposed on it in the usual experimental procedures It is also at least conceivable that the net results of heavy dosages are not only quantitatively but qualitatively different from those that would result from doses that might be considered to be quantitatively comparable with the changes brought about spontaneously in the ordinary course of the animal's life

During the progress of the research there has accumulated incidentally to the main purpose a considerable body of data that may be of interest to those who desire to measure the potency of insulin preparations It will not be out of place to consider these data from the standpoint of insulin assay

#### METHODS

Rabbits were used exclusively as subjects The animals were obtained in the open market and were selected only in regard to physical condition No attention was paid to breed or sex<sup>2</sup> When purchased, they weighed about 2 Kg and were in early sexual maturity After purchase, they were kept for at least two weeks on the regular regimen before they were used in experimental work They were not subjected to experimental use oftener than once a week, with the exception that in some of the earlier work three days were allowed to elapse after the control observations and after the administration of light doses of insulin, as  $\frac{1}{8}$  or  $\frac{1}{16}$  of a unit per kilogram With heavier doses, the seven day rest interval

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<sup>2</sup> Scott, E L Reducing Power (Blood Sugar) of Filtrates from Blood of Rabbits, Arch Int Med 43 393 (March) 1929

was allowed throughout the research. The animals were kept in use so long as they remained in good condition. Some were in use for more than two years, and several attained a weight of 3.5 or 4 Kg.

In the earlier part of the work they were kept in pens with a considerable floor area, six or eight animals being kept together in a single pen. During the greater portion of the work, however, the rabbits were confined in individual cages, 12 by 15 by 20 inches.<sup>3</sup> The latter system proved to be much more satisfactory since a considerably greater precision was obtained, although the results were not otherwise appreciably altered. The animals also remained in better condition and, on the average, lived longer in the individual cages than they did in the larger pens.

In that part of the earlier work in which consecutive samples were obtained the animals were fed up to the beginning of the experimental procedures, with the exception of two series, the specific purpose of which was to investigate the effects of inanition. In the remainder of the work an inanition period of about eighteen hours preceded the injections.

The research has run through a period of seven years and through a removal from one laboratory to another. As a consequence of this there have been different regimens in the diet of the animals. The diet has, however, at all times permitted what appeared to be a normal growth of immature rabbits and a full maintenance of weight in all fully grown adults. The relation of the type of diet to the effect of the insulin will be more fully discussed in a later section.

It was the custom to bring the animals to the laboratory about an hour before the beginning of the actual experimental procedures. The blood samples were obtained from the marginal ear vein after the ear was well coated with petrolatum. Hyperemia was induced by massage, or when necessary, by the application of xylene. The blood was caught in a small dish which had been dusted with powdered sodium oxalate.

The blood proteins were precipitated with phosphotungstic acid, and the sugar in the filtrate was determined by the method described by Shaffer and Hartmann.<sup>3</sup> The conversion table published by Duggan and Scott<sup>4</sup> was used for determining the sugar content of the sample.

The insulin used was the product of three different manufacturers. It was purchased in the open market in 100 unit ampules in a concentration of 20 units per cubic centimeter. The stock was kept in a refrigerator except for the time that it was in actual use in the laboratory. After being brought to room temperature, it was diluted with 0.9 per cent sodium chloride solution so that 1 cc of the resulting mixture contained the amount to be injected per kilogram of animal weight. The volume injected, then, was always 1 cc per kilogram, regardless of the dosage. A new dilution of insulin was made daily, unused portions being discarded. The injections were made subcutaneously in the region of the flank or the abdomen.

#### CONTROLS

The two major difficulties that have arisen in the study of the effects of light dosage with insulin have been mentioned. One, the question of the presence of some compensatory mechanism within the animal, is, of course, purely a problem for physiologic investigation. The other is the difficulty of differentiating those changes in the blood sugar level

<sup>3</sup> Shaffer, P. A., and Hartmann, A. F. *J. Biol. Chem.* **45**, 365, 1921.

<sup>4</sup> Duggan, W. F., and Scott, E. L. *J. Biol. Chem.* **67**, 287, 1926.

that occur spontaneously from those that are due to the insulin that has been administered. The latter is a problem in the precision of measurements and must be attacked from that standpoint.

There are two general methods for increasing the precision of a measurement. First, and most important, is the standardization of the material and of the technical procedures. The second method consists in multiplying the number of observations until statistical treatment is permitted.

One of us <sup>5</sup> has shown that in blood sugar studies on rabbits a group of fifty observations is sufficient to warrant statistical treatment and interpretation within certain determinable limits. In compliance with this, each point on every curve discussed in this paper indicates the mean of at least that number of observations, unless the contrary is specifically indicated.

The matter of the standardization of the material is somewhat more difficult, since it not only involves the original selection of the individual subjects, but also their entire subsequent care, indeed, their whole history, both before and after their entry into the laboratory. Much of this history which is pertinent cannot be known to the experimenter and undoubtedly is an important factor in the "spontaneous" variations with which all are acquainted. However, we feel that with the exercise of what care we were able to employ in the standardization of material and technic, together with the repetition of measurements, we were able to attain a precision sufficient to justify certain conclusions.

In measuring precision, we have employed the mean deviation,  $\epsilon = \sqrt{\frac{\sum x^2}{N-1}}$ , rather than the standard deviation,  $\sigma = \sqrt{\frac{\sum x^2}{N}}$ , for the reasons outlined by Scott <sup>5</sup>. The following derivatives of the mean deviation are also employed:

The mean deviation of the mean  $\epsilon_M = \frac{\epsilon}{\sqrt{N}}$

The mean deviation of the difference between two means  $\epsilon^{B-A} = \frac{\epsilon^2_B + \epsilon^2_A}{\epsilon^{B-A}}$

The mean deviation of quotients  $\epsilon_{\frac{B}{A}} = \frac{\sqrt{\left(\frac{B\epsilon_A}{A}\right)^2 + \epsilon^2_B}}{A}$

Two types of controls were used. In the earliest work we followed a procedure which, for brevity, we shall refer to in further discussion as the method of consecutive sampling. In this method a blood sample was taken before the insulin was injected, and further samples were taken at stated intervals after the injection. The initial sample constitutes the control with which the later samples are to be compared. The accuracy of this form of control was checked by running a complete

<sup>5</sup> Scott, E. L. J. Biol. Chem. **73** 81, 1927

series of fifty observations in which only the appropriate quantity of an isotonic solution of sodium chloride was injected. The blood samples were then taken as in a regular experiment. The results of this series indicate that, quite apart from any direct effect of the insulin, it is very probable that the concentration of sugar in the blood is influenced by the experimental procedures necessary. The method, then, is open to criticism, for, if the later samples are modified by the process of taking the earlier samples, there must be a question as to the amount of this modification in each case and of the allowance that should be made for it in estimating the true effect of the insulin. A determination of the probable extent of such modifications would constitute a respectable research in itself.<sup>6</sup>

Consequently, the method of control by consecutive samples was abandoned early in the research, and the method described in one of the papers just cited<sup>2</sup> was substituted for it. This method, for brevity will be referred to as the method of "independent series." In theory, it is based frankly on the principles of probability. The assumption is made that if a definite group of rabbits is cared for in a definite manner, and if the number of individuals and of observations is sufficiently large to justify statistical prediction, it may be expected that averages of observations made at different times will agree with one another within certain determinable limits. Before we ventured to make use of the method, however, it was put to experimental test and was found to hold to an unexpected precision. The details of this work were reported by Scott.<sup>7</sup> From the data published there it is shown that the mean blood sugar value of a group of rabbits for a given time may be predicted within determined limits. If, now, the conditions are altered by a single factor, as by the injection of insulin, and if the average concentration of sugar in the blood varies from the predicted value by more than the determined limits of precision, the difference may be attributed fairly to the effects of the insulin. This method offers the possibility of studying the effect of the insulin with a minimum number of disturbing factors. The conditions under which the control and experimental observations are made may be as nearly identical as is humanly possible, except for the fact that in the control group the animals were given injections of salt solution, while for the other group a similar volume of salt solution carried a certain amount of insulin.

Changes in the character of the material being studied, i. e., the rabbits, may be expected to engender changes in the initial level of the blood sugar concentration. Such modifications of the sugar value might very well arise through changes in the individuals subjected to study, or through changes in nutrition, temperature or other modifications in

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<sup>6</sup> Scott (footnotes 2 and 5)

<sup>7</sup> Scott (footnote 2, table 6)



the environmental conditions. For this reason it is necessary, when a high degree of precision is required, to accompany each experimental series of observations with a similar control series, both sets of observations being made on the same subjects.

In comparing the potency of two samples of insulin or in studying the effects of different dosages, we have frequently made up a series in the following manner:

Day of Observation	Experimental Condition
1st	First control
8th	$\frac{1}{8}$ unit, insulin sample A
15th	$\frac{1}{4}$ unit, insulin sample A
22d	Second control
29th	$\frac{1}{8}$ unit, insulin sample B
36th	$\frac{1}{4}$ unit, insulin sample B
43d	Final control

It will be noted that a week intervenes between any two consecutive observations. This is thought to be desirable to insure complete recovery from the effects of previous treatment. Observations are included in the final average only when the subjects studied were in a satisfactory condition throughout the period of observation. Each insulin group is adjacent to a control group and is situated between two such groups. Further, it was our intention to discard an entire series if the control groups did not agree with one another, within the limits set by statistical theory. Such a procedure was unnecessary, however, for in only one case did a lack of agreement to this degree exist, and in that one case it was necessary to discard the group because of other accidental conditions which vitiated the similarity of the component parts. It is evident from the make-up of such a series that the number of observations must be the same for each of its component parts.

#### THE INSULIN TIME AND DOSAGE CURVES

The purpose of the time curves is to follow the blood sugar changes through a short period subsequent to the administration of several different doses of insulin. It was hoped that a study of such curves would reveal some constant characteristic that might be used in measuring the dosage of insulin.

In this work the method of consecutive sampling was made use of, for, though this method, as was pointed out in the section on "Controls," does not permit of as high a degree of accuracy as does that of independent series, the accuracy is sufficient for purposes of exploration, and this method is more rapid and less expensive than the other. In general, the curves shown in this paper are plotted in terms of percentage change in blood sugar rather than in absolute levels or in

absolute changes in level. The advantages of this form of presentation will be discussed in the section on "The Criteria of the Insulin Effect."

The results for six different doses are shown in charts 1 and 2. These charts show (a) that, given a considerable number of observations, the several points may be determined with a fair degree of precision, (b) that the duration as well as the degree of hypoglycemia is related to the dosage, (c) that the curves for the lighter doses are well on the way back to the original level some time before those for the heavier doses have ceased to fall (an important point, the neglect of which occasionally gives rise to misleading statements in the literature) and (d) that, with the lighter doses, at least, there may be a late hyperglycemia, occurring when the returning curve overshoots the original sugar level. This reminds one of the hypoglycemia so commonly seen in dextrose tolerance curves, though, of course, it is the reverse phenomenon.

It is also instructive to modify the foregoing method of procedure so that the dextrose change for each of the time intervals studied is plotted against the several doses. This has been done in chart 3. When plotted in this manner the resulting dose curves vary in the degree of change, and in addition to this it should be noted that there is a wide variation in the form of the curves. Both of these points are of great importance in assay work, as will be brought out in the following section.

With the shortest observation period (three fourths of an hour), there results a reasonably smooth curve. At the next period (one and one-half hours), though the form of the curve is, perhaps, even more satisfactory, there has been a noticeable return toward the original (normal) value for the lighter doses, while the points for the medium doses hold their position and those for the heavier doses continue to fall. This all leads to a greater distribution of the points and so to the simulation of an increased sensitivity. This is, however, only simulation and is misleading, for it arises from the fact that the full effect of the lighter doses is missed, due to their early recovery, and consequently their effect is minimized, in relation to the others. So, though the scale is extended, the curve is distorted. After two and one-half hours the point for the lightest dose is back at the original level, so that no change is indicated, while there has been some return for each of the other doses employed. The degree of the return is, however, more marked with the medium doses than it is with the heavier ones. At three and one-half hours the point for the lightest dose is well beyond the original level, while those for the next two doses have returned almost to this level. All of the various characteristics of the several curves must be considered in

formulating any system designed for the measurement of the effect of the insulin through the determination of the concentration of the blood sugar

#### THE CRITERIA OF THE INSULIN EFFECT

Before proceeding further, it is in order to select a criterion on which to base our estimation of the effect of insulin. Our primary interest lies in changes in the concentration of sugar in the blood which may be associated with changes in the concentration of insulin in the blood, whether the latter have arisen spontaneously or through the administration of insulin. That change in the blood sugar should be sought that is most intimately related to the activity of the insulin and is least affected by other factors. To be satisfactory, this change must appear with slight as well as with profound changes in the insulinemia. In administration of insulin the blood sugar changes must vary in proportion to the variations in the amount of insulin that has been administered. The curves shown in charts 1, 2 and 3 reveal several characteristics which might, a priori, be selected for this purpose.

(a) *The Optimum Time Interval*—In estimating the effect of the insulin through the determination of blood sugar change, the first problem to arise is that of choosing the proper time interval between the administration of the insulin and the taking of the blood sample. In each of the curves, shown in charts 1 to 3, a very definite minimum sugar level appears. Probably the interval between the injection of the insulin and the appearance of this minimum level will occur to the investigator as the most desirable one to employ. Closer study, however, makes evident several difficulties which render this particular interval impractical. First, although the average time interval may be fairly constant in a particular group of individuals subjected to a particular set of environmental conditions, there is found to be a considerable individual variation within the group. This difficulty was early noticed by Macleod, and it is the experience of all workers in the field. It follows that, unless a number of blood samples are taken at comparatively short intervals, it is possible only occasionally to secure a sample of blood exactly on the appearance of the minimal value. Failure to secure the sample at the exact moment of the minimum must necessarily result in sugar values that are higher than the minimum. It also follows that it is not possible to determine the minimal value by the method of averages, for the minimum is a limiting value, and while chance observations may be made during the period of the lowest sugar value, the majority will either precede or follow this period. In either case, values somewhat higher than minimal values must result. On the other hand, no values below the minimal can be obtained. Any average value must, then, be in excess of the true minimal value.

Another objection to the use of the interval between the administration of the insulin and the appearance of the minimal value, which is quite as serious as the one just discussed, results from the fact that this interval varies with the insulin dose, becoming progressively longer as the dose becomes larger. It results from this that where the purpose of the observations is to determine changes in the degree of insulinemia that are related to physiologic changes or conditions, the method must be used with caution, for, as the degree of insulinemia is unknown, it follows that the time interval which should be allowed between the stimulus and the removal of the blood sample must also be unknown.

One might think, on the other hand, that where the purpose of the observations is to measure the potency of an insulin preparation, it would be possible to determine the proper interval with sufficient accuracy by means of preliminary observations. It is possible that such a procedure might be permissible, but it must be borne in mind that the interval may be expected to vary from time to time in a particular individual as well as from individual to individual. So even in this case the method would be attended with a certain inaccuracy, and the final average blood sugar must be higher than the minimum.

As has already been mentioned, it is possible to draw a series of blood samples at short intervals and to use only the one that gives the lowest sugar value. That is, it is possible to obtain data for each subject that would permit the construction of a curve for each individual such as those shown for groups in chart 1. In this manner it would be possible to obtain the actual minimal value, except for the effects of the necessary technical procedures as were discussed in the section on "Controls." In addition to these physiologic objections, the technic involved in such a procedure would be very burdensome because of the excessive number of determinations it would necessitate.

In order to mitigate these objections in some measure, it is the practice in one of the standard methods for insulin assay<sup>1</sup> to draw only three samples of blood at stated intervals and to use the mean value of these determinations as the criterion sought. It is true that this modification greatly reduces the number of observations, but the time curves in charts 1 and 2 show that unless the dosage is known to a fair degree of approximation very misleading conclusions may be drawn from results so obtained. This is especially true for light doses and might, in such cases, easily result in the conclusion that insulin causes a fall in blood sugar, or that it causes no change or even that it causes a rise, depending only on the dosage and the particular time intervals which happen to have been employed in the observation. It would appear, then, that in this procedure the accuracy of the final value is so far sacrificed in order to obtain better physiologic conditions

and for technical convenience that when the dosage is unknown little of practical use can be learned from it, this is certainly true for the lighter doses

It is difficult to see how the use of the minimum blood sugar value as the criterion may be made practical, for it cannot be determined by averages, nor located by a single determination, while a series of determinations is impractical, both physiologically and technically. It is, consequently, necessary to extend the search for a practical measure of blood sugar change

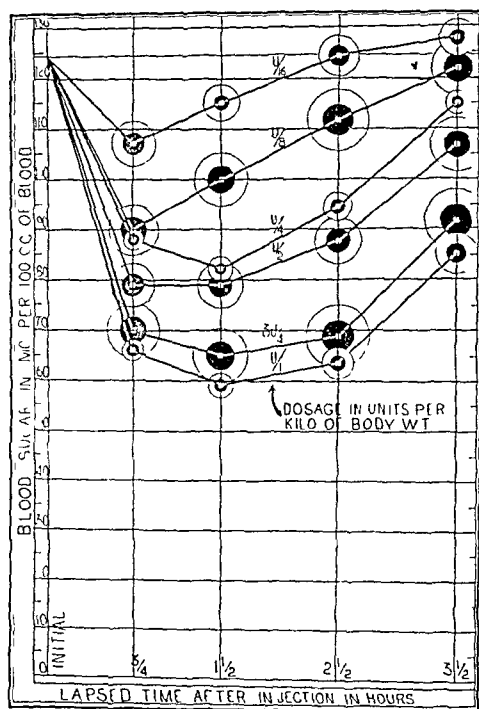


Chart 1—Time curves for different dosages of insulin. For convenience in comparing the data, all of the values were adjusted to terms of the mean initial value of 123 mg per hundred cubic centimeters. The circles indicate the precision with which the several points were established. The radii of the black circles correspond to  $\epsilon_v$ , those of the outline circles, to  $2\epsilon_M$ . The data were obtained by the method of consecutive samples. The points on the curve for  $\frac{1}{4}$  of a unit and for 1 unit were established from about one hundred and fifty observations each. The remaining points were established from fifty observations.

As was shown in the section on "Controls," the use of a single sample of blood is preferable on both physiologic and technical grounds and is permissible on the basis of its statistical significance if proper precautions are taken. The question then arises as to whether there may not be some point on the curve, other than the minimum, which could be established legitimately by averages. The practical definition of such a point must be in terms of time rather than of blood sugar level,

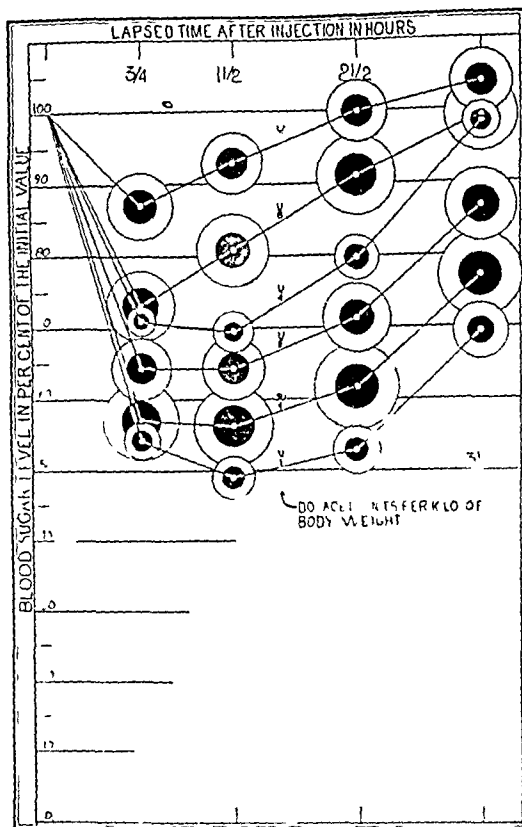


Chart 2—Time curves for different doses of insulin The same material as is shown in chart 1, plotted in terms of the *relative* concentration, i e, the concentration is plotted in terms of per cent of the initial concentration, instead of in terms of the absolute values as in chart 1

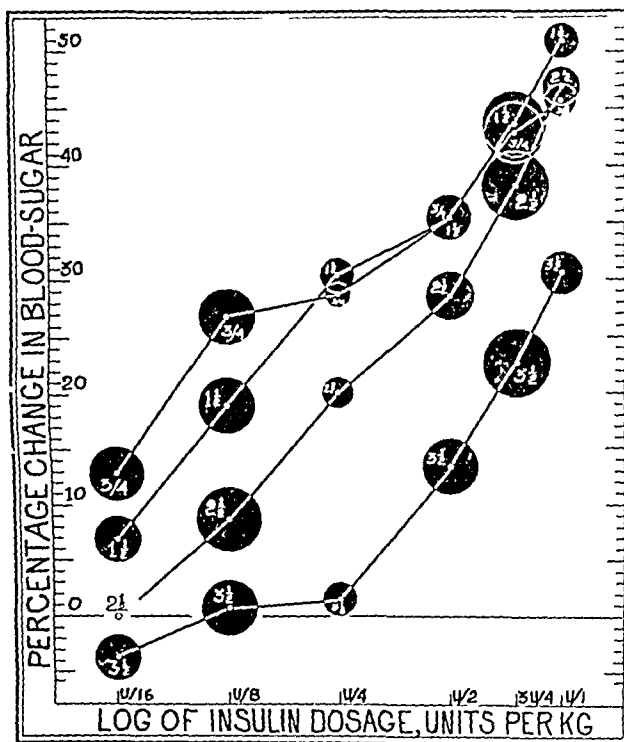


Chart 3—Dose curves for different time intervals This chart was plotted from the same material as is shown in charts 1 and 2 The precision is indicated by the circles, the radii of which indicate 2  $\sigma$  The figures within the circles indicate the interval, in hours, between the administration of the insulin and the drawing of the blood sample

since any point defined in terms of blood sugar will involve many of the same difficulties that were encountered in the determination of the minimal value

The selection of a definite interval after the administration of the insulin at which the sugar level shall be determined amounts to a determination of the rate of blood sugar change rather than a measure of the absolute change. Of course, the rate of change over any portion of the curve might, theoretically, be selected for this purpose, but an initial period has been chosen as the one which probably would be the most convenient and at the same time give the desired information with the greatest precision and accuracy.

By strict theory, the time of drawing the blood samples should be so chosen for each dose that the maximum initial velocity of change will be measured. Reference to the time curves (charts 1 and 2) will show that the time at which this maximum velocity of change occurs becomes longer as the dose is increased. From this it follows that if the maximum rate of change is to be measured the time which is allowed to elapse between the administration of the insulin and the drawing of the blood sample must be adjusted to the dose which has been administered. As the strength of the dose is unknown, since it is this that is being determined, it follows that the appropriate time interval is also unknown in any particular instance, and so this method, also, becomes impractical.

The possibility of the study of the initial rate of change for a predetermined period, which is the same for all doses, still remains. Although the rate, determined in this manner, cannot be considered as the maximum rate for all doses, the interval may be so chosen that there is a fair degree of approximation to the maximum over a considerable portion of the practical dose range.

The interval chosen should be such that the curves for the higher doses are just beginning to flatten out for the minimum level. At this time the average rate of change for the entire dose range will be somewhat less than the maximum. This arises because this flattening of the curves for the light doses occurs before those for the heavier doses have reached their maximum, so that both the lightest and the heaviest doses will show less than their maximum effect. The choice of such a period obviously is a compromise and must involve a certain amount of inaccuracy in the determination of the effect of the insulin, since very low and very high doses will both be somewhat undervalued when the interval is adjusted to give correct values for the intermediate range. However, the objections to this procedure seem to us to carry less weight than do those that may be offered against any of the other methods that we have seen proposed or that we ourselves have been able to devise.

As yet there is not a satisfactory body of data to warrant an attempt to calculate this "optimum" interval. It becomes necessary, therefore, to resort to judgment, on the basis of experience, for its choice. On this basis an interval of thirty minutes was selected as probably being very near to the optimum. Empiric results seem to have justified the choice.

(b) *The Most Characteristic Function of the Blood Sugar Change*—If it is assumed that the most satisfactory procedure for sampling the blood is to draw a single specimen thirty minutes after the administration of insulin, there remains to be determined the particular function of the sugar concentration of this blood, which most precisely and accurately indicates the effect of the insulin, while it, at the same time, is relatively independent of other influences.

Two methods, which differ fundamentally in their physiologic implications, have been employed in estimating the effect of insulin on the concentration of sugar in the blood.

The method proposed by one school assumes that a definite subnormal level will be attained as the result of a definite dosage of insulin. This level, it is assumed, will be attained regardless of what the initial blood sugar level may have been. The opposed school assumes that the minimal level is in some manner related to the initial concentration. Here, again, there are two possibilities. First, it may be assumed that with a definite dose of insulin the minimal level will differ from the initial level by an amount that is determined only by the amount of insulin that has been administered and that is independent of the initial level. Second, it may be assumed that the difference between the initial and the final levels is determined, in some manner, by both the insulin dosage and the initial blood sugar concentration.

Recapitulated, the three concepts may be represented as follows:

- (a) The final blood sugar concentration is a constant for a given dose.
- (b) The difference between the initial and the final blood sugar concentration is a constant for a given dose.
- (c) The ratio of the difference between the initial and final values to the initial value is a constant for a given dose.

Each of these three possibilities has been considered in the literature, but the weight of practice seems to favor the first or the second. The third possibility has, for the most part, received but scant consideration.

If the first suggestion is true, there should be a very low coefficient of correlation (Pearson's "*r*") between the initial and the final (thirty minutes after insulin) blood sugar concentrations, and a very high correlation between the initial concentration and the absolute difference between this and the final concentration due to insulin. The pre-



ceding statement would follow from the fact that the final concentration would, on this assumption, have a definite value. This value would be dependent on the insulin dosage alone and would be wholly independent of the initial value. Thus there would be no correlation between the initial and the final values, and  $r$  would necessarily be very low. Theoretically, it would be zero. On the other hand, the absolute differences between the admittedly variable initial and the assumedly constant final values must vary directly with the initial values. The consequence of this is that  $r$  must in this case approach its maximum value. Theoretically, it would be 1.

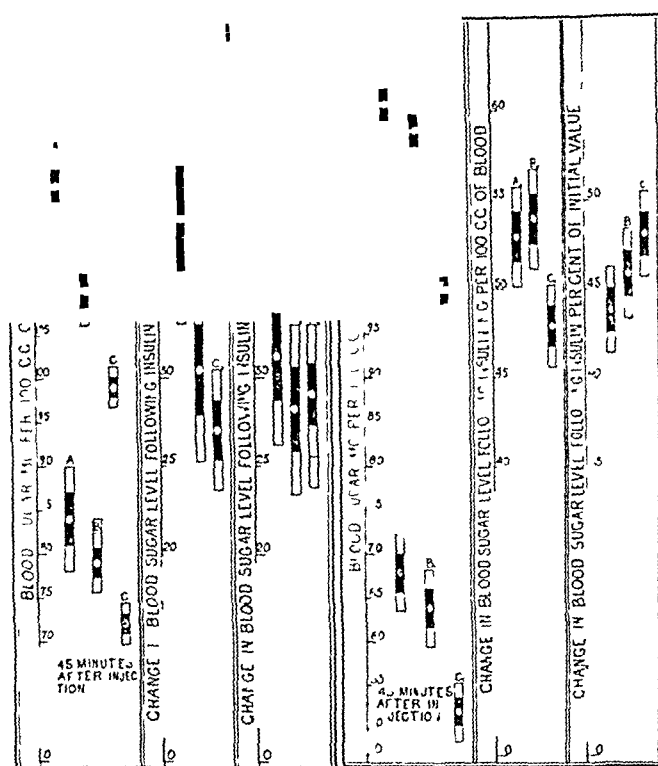
On the basis of the second assumption, a similar line of reasoning will show that there must be a high correlation between the initial and the final concentrations, while there should be a very low correlation between the initial level and the absolute difference between this and the final level. For now this difference is considered to be the definite constant value dependent only on the insulin dosage and wholly independent of the initial concentration. However, if the difference is constant, the final level must vary directly as does the initial.

If it is assumed that a given dose of insulin lowers the blood sugar concentration to a constant level or lowers it by a constant amount, then the other value must vary directly with the initial blood sugar. Further, the coefficients of correlation between these values and the initial must be very high for one and very low for the other, since the variations of the one which is dependent on the initial must have the same absolute values as do the variations of the initials themselves.

On the other hand, if it is assumed that a definite dosage of insulin will change the blood sugar concentration by a definite percentage of itself, it will result that both the final concentrations and the differences between these and the initial values will vary in the same direction as the initial amounts, but each will vary by lesser absolute amount than do the corresponding initial values. It would result from this that both the coefficients of correlation between these two values and the initial amount would take an intermediate place, since the variations of the initial values are now divided between the respective finals and differences. On the other hand, if the relative decrease depends only on the dosage of insulin, then one would expect to find a very low coefficient of correlation between the relative decreases and the initial values.

These coefficients of correlation have been examined for two groups of one hundred and fifty observations each, in which the initial blood sugar values varied over an unusually wide range. This variation of the initial values was accomplished by nutritional manipulation and, so far as we could tell, did not at any time exceed what we are pleased to term physiologic bounds.

In one of these experiments the initial blood sugar varied from 80 to 150 mg per hundred cubic centimeters. The correlation, as represented by  $r$ , between the initial value and the value forty-five minutes after the injection of  $\frac{1}{4}$  of a unit of insulin per kilogram of body weight, was 0.63, between the initial and the absolute decrease, it was 0.48, and between the initial and the relative decrease, it was only 0.11. The former two values of  $r$  are therefore intermediate, while the latter value may be considered to be so small as to be within the limits of variation and so to have no interpretable meaning.



Charts 4—These charts were devised to illustrate the dependence of both the blood sugar concentration and the absolute drop forty-five minutes after the administration of insulin on the initial concentration, and the independence of the relative drop and the initial value. In each chart  $A$ ,  $B$  and  $C$  represent the initial blood sugar levels for three different groups of observations,  $A_1$ ,  $B_1$  and  $C_1$ , absolute blood sugar level forty-five minutes after insulin,  $A_2$ ,  $B_2$  and  $C_2$ , the absolute change in level at this interval,  $A_3$ ,  $B_3$  and  $C_3$ , the corresponding percentage changes. The dosage was  $\frac{1}{4}$  of a unit per kilogram of body weight for the data shown in  $a$ , and 1 unit per kilogram for those shown in  $b$ . Each point was established by fifty or more observations. The precision is indicated by the vertical bars, the black portion representing  $\epsilon_M$ , and the outline portion  $2\epsilon_M$ .

In the other experiment the rabbits were given 1 unit of insulin per kilogram instead of  $\frac{1}{4}$  of a unit, and the blood samples were taken as before, forty-five minutes after the injection. The correlation coefficients were all of the same order. The only striking difference was that

the coefficient for the correlation between the initial and the relative decrease was in this case a negligably small negative number. This change in the sign, together with the very small values of these two coefficients, makes the conclusion all but final that there is in fact no correlation at all between the relative drop and the initial

Thus all of the coefficients of correlation are just such as would be expected on the basis of the third assumption, intermediate correlations being found for the absolute values, while no significant correlation exists between the initial and the relative change. Therefore, we may conclude that the relative change is independent of the initial blood sugar value and wholly dependent on the insulin dosage.

The results of these experiments are shown graphically in chart 4.

(c) *The Nature of the Proportionality Between the Blood Sugar Change and the Insulin Dosage*—Reference to charts 5 and 6 will show that the proportionality that exists between the blood sugar changes and the dosage of insulin is not a direct one, but that over a considerable portion of its course it follows a logarithmic relationship with surprising precision. It is important to note, however, that the proportionality actually is limited in its range. No doubt one factor that underlies this loss of proportionality in the upper reaches of the curve arises from the fact, noted in paragraph *a*, that the blood samples are drawn prior to the appearance of the maximum rate of fall for these doses, while it is closely approximated in all of the lighter doses for which determinations were made. However this may be, it is possible that this is not the complete explanation, and a better understanding of the reasons for this limitation may prove to be of fundamental importance in developing a theory of carbohydrate metabolism. At present, though, we are not competent to enter on a theoretical discussion of the significance of the lack of complete proportionality, nor for the matter of that of the proportionality itself. It should be noted, though, that on the basis of the foregoing reasoning, a similar flattening of the curve is to be expected in the extreme low reaches of the curve because here it is probable that the samples have been taken after the inception of the return to the original level.

(d) *The Optimum Magnitude of the Insulin Dose*—In addition to the loss of proportionality in the upper ranges, the useful portion of the curve is still further limited by the fact that the proportionality, where it exists, is logarithmic and not direct. This so affects the precision of the determinations for the heavier doses that it is not practical to differentiate the effect of one dose from that of another. At the other extreme, the precision of our best methods for the determination of blood sugar does not permit us to differentiate the sugar concentrations of blood after very small doses from those of the controls.

Chart 6 shows that the logarithmic proportionality begins to fall at a dosage somewhat less than 1 unit per kilogram. Extremely heavy dosage will hardly force a drop of more than 50 or 60 per cent of the initial value, even though a much longer interval be allowed to elapse before the blood sample is taken. Doses of  $\frac{1}{16}$  of a unit per kilogram will cause a drop of 10 to 15 per cent of the initial at the end of thirty minutes. Double this dose, i. e.,  $\frac{1}{8}$  of a unit, will cause approximately double the relative drop, somewhere between 25 and 30 per cent, but should the dose be doubled again, that is, should  $\frac{1}{4}$  of a unit be given instead of  $\frac{1}{8}$ , the relative drop is only about 35 per cent of the initial

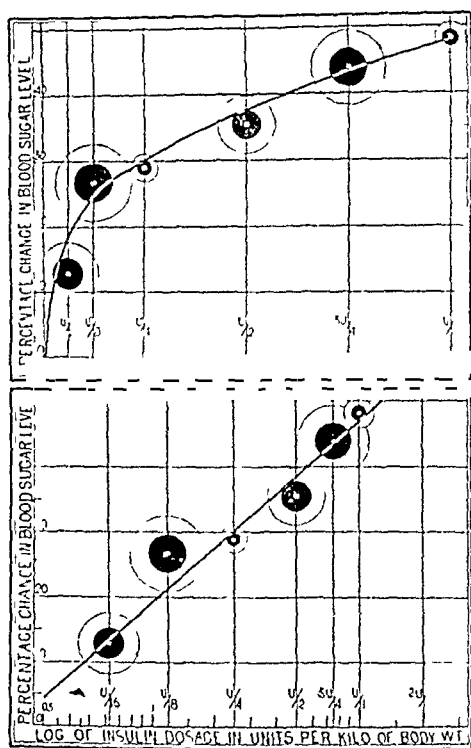


Chart 5—The percentage changes in the blood sugar level forty-five minutes after administration of insulin plotted against the dosage. The material is the same as was shown in chart 1. In the upper figure the relative changes are plotted against the natural values of the dosage, while in the lower figure they are plotted against the corresponding logarithms. The precision is indicated as in chart 1.

The expected effects of doses of  $\frac{1}{2}$ , 1 and 2 units per kilogram are, respectively, drops of 43, 50 and 53 per cent of the initial values. In other words, the relative drop for a dose of 2 units is only 23 per cent greater than that for  $\frac{1}{2}$  of a unit. The corresponding changes for doses of  $\frac{1}{16}$ ,  $\frac{1}{8}$  and  $\frac{1}{4}$  of a unit are respectively, 18, 27 and 35 per cent. That is, increasing the dosage by  $\frac{3}{16}$  of a unit, from  $\frac{1}{16}$  to  $\frac{1}{4}$ , will cause a greater disturbance in the blood sugar level than increasing the dosage by  $1\frac{1}{2}$  units, from  $\frac{1}{2}$  to 2. It would seem to be obvious,

then, that in the interest of precision the dosage should be kept as low as is consistent with an appreciable change in the blood sugar level. One eighth and  $\frac{1}{4}$  of a unit per kilogram are suggested as two very satisfactory dosages with which to work. In any case, the dosage should not greatly exceed  $\frac{1}{2}$  of a unit per kilogram, because the loss of proportionality begins to become apparent in this region. On the other hand, it should not be much below  $\frac{1}{16}$  of a unit because of the difficulty of differentiating the small changes that might arise as a result of the insulin from the spontaneous changes which might arise from uncontrolled causes.

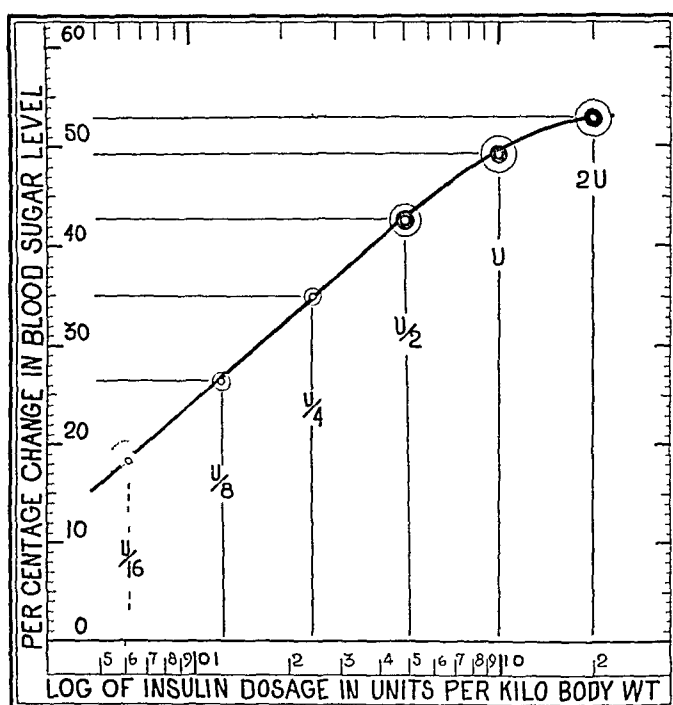


Chart 6—The percentage drop thirty minutes after administration of insulin, plotted against the logarithm of the dose. The point for  $\frac{1}{16}$  of a unit was established from fifty observations, that for  $\frac{1}{8}$  of a unit from three hundred, for  $\frac{1}{4}$  unit by four hundred, and the remaining points from one hundred observations each. The data were obtained by the use of seven samples of insulin, the product of three different manufacturers. Control was by the method of independent series. The precision is indicated as in chart 1.

#### NUTRITION AND THE INSULIN EFFECT

From time to time papers have appeared in which it is claimed that one or another dietary regimen influences the response of the animal to insulin. Though, in the present researches, careful attention has been given to the diet at all times, convenience or necessity has occasionally determined its modification. While every effort has been made

to keep any given dietary regimen constant through its course, there have been, in fact, several different regimens in the duration of the research. Occasionally, modifications of the mean initial sugar level have appeared which, seemingly, were associated with these changes in the diet. Associated in turn with the modifications in the initial blood sugar level, we have found the modifications in the final values and in the absolute drop due to the insulin, which would be expected from the discussion on the section on "The Criteria of the Insulin Effect." However, we never have had any evidence that the relative drop in the blood sugar level was in any manner modified by the nature, or by the

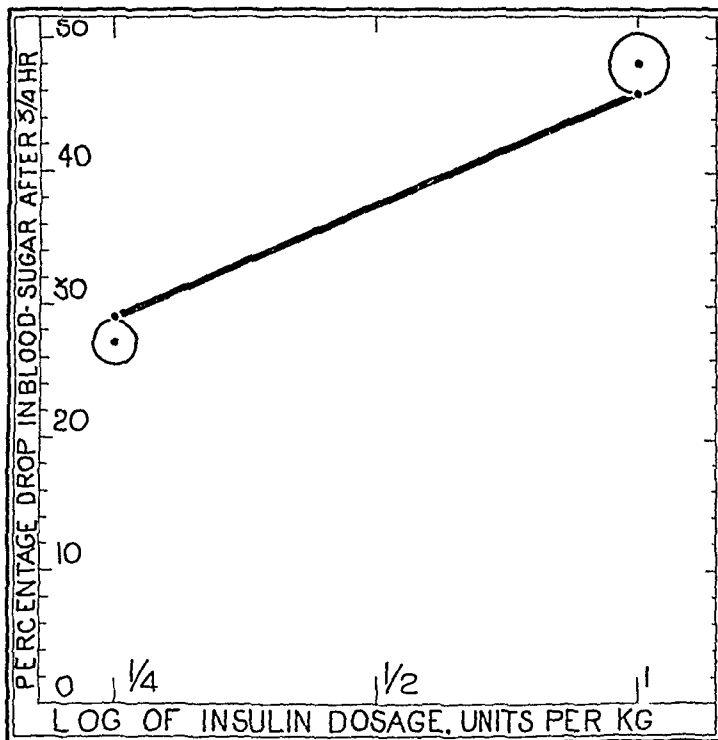


Chart 7—A diagram to illustrate the apparent lack of influence of inanition on the effect of the insulin, when this is estimated from the relative change in blood sugar concentration. The bar represents the mean effect, as shown by one hundred and fifty observations on full fed rabbits, for each of the two points established. The dots show the effect of corresponding doses after eighteen hours of inanition. The precision with which the points on the bar are established is indicated as in chart 5. The points after inanition were established from fifty observations each. The radii of the circles indicate  $\epsilon_v$ .

amount of food consumed, even though this amounted to short periods of complete inanition. A comparison of the effects of insulin after eighteen hours of starvation, with its effects on the full fed subject, is shown in chart 7.

There are two reasons, either of which might lead one to subject rabbits to a short period of inanition before using them in insulin

studies, and particularly for insulin assay. In the first place, the nutritional condition of different subjects may be presumed to be more uniform, and consequently any effects that the insulin might have may be expected to be more uniform through a group of subjects in starved animals than would be the case in animals permitted to eat as they desired. The second consideration probably results directly from this increased uniformity in the nutritional condition of the individuals of the group. It is, simply, that the initial blood sugar values of starved animals have been found to be slightly less variable than are those of well fed animals. The ideal period of inanition for insuring this increased precision appears to be from eighteen to twenty-four hours.<sup>2</sup> It should be noted, however, that the initial blood sugar concentration is somewhat lower under these conditions than it is in the more "normal" full fed animal. It would follow from this, in assay work, that when the assay is based on the absolute final blood sugar level, a somewhat greater precision may be obtained when food is withheld from the subjects for a short time than is possible when working with full fed animals. It should also be noted in this connection that with the lowered initial level there will be an apparent increase in the sensitivity to insulin. This is, however, only apparent and cannot be of any aid in increasing either the precision or the accuracy of the assay. It results from the fact that the absolute final level will be somewhat lower after inanition than otherwise, because of the lowered initial level. One result incidental to this is a relatively high incidence of insulin shock, as compared to that resulting from the same dosage in full fed subjects. Thus, in one series of fifty observations there were eleven cases of convulsions when the animals were full fed and twenty-six cases when the same animals were given the same insulin dosage after eighteen hours' inanition.

In any case the difference in precision is small, and when the assay is based on the relative, rather than on the absolute, change, it becomes negligible or, indeed, altogether absent. All considerations taken together, it is questionable whether the accuracy of an assay is increased by subjecting the animals to inanition in spite of the admitted increase in precision and the apparent increase in sensitivity.

#### THE RELATION BETWEEN THE BODY WEIGHT AND THE INSULIN EFFECT

In the Toronto method of insulin assay the attempt is made to inject a constant dose into subjects of a constant weight. Thus, when the system is adhered to strictly, the question of the relation of body weight to dosage does not arise. However, in actual practice it is frequently difficult or inconvenient to have all of the animals of precisely the same

weight, and it would be of great assistance if a system could be developed which would permit of some latitude in the weight of the animals

The statement that the sensitivity of the animal to insulin varies inversely as the square of its body weight is attributed to Watters. Thus it is said that a 2 Kg rabbit requires four times as much insulin to induce shock as would be required by a rabbit weighing only 1 Kg. If, however, the procedure is so changed that the dose is measured in terms of units per kilogram of body weight instead of in units per individual, it will be seen at once that if each of the aforementioned animals were given the same number of units the heavier rabbit would receive but half of the dose per kilogram that would have been given to the lighter one. Now, if it is granted that the effect of insulin is measured by the logarithm of the dose per kilogram of body weight, the underlying reason for Watters' observation is readily understood.

The relation between the weight of the rabbit and the insulin effect was studied in two series of one hundred observations each. In the first of these groups the rabbits studied varied in weight from 1.5 to 4.25 Kg. The average percentage blood sugar drop forty-five minutes after the administration of  $\frac{1}{4}$  of a unit per kilogram was  $30 \pm 1$  per cent of the initial. The coefficient of correlation ( $r$ ) between the body weight and the relative drop for this group was  $-0.04$ . The second group varied in weight from 1.75 to 4.25 Kg. The percentage drop in the blood sugar concentration forty-five minutes after 1 unit of insulin per kilogram was given was 45 per cent  $\pm 1$  per cent,  $r$  was  $-0.01$ . These values of  $r$  are certainly so small as to be within their limits of error, and the conclusion is justified that when the dose is measured in units per kilogram of body weight the effects of the insulin are strictly comparable, within the limits already set, and that no further consideration of the body weight is required. Note, however, that our evidence was obtained on sexually mature rabbits. What would happen in the case of light rabbits when the small body weight is due to immaturity we are not in position to say.

It follows directly from this that, provided that they are otherwise similar, it is legitimate to include rabbits of greatly varying weight in any series of observations based on the system that we have outlined. If one considers the difference in the systems of measuring the dosage, Watters' statement is fully confirmed.

#### THE BEARING OF REPEATED DOSAGE ON THE INSULIN EFFECT

The question of the effect of the insulin dosage on the subsequent sensitivity of the individual to insulin is one that frequently arises. Obviously this is a matter of great importance from both the theoretical



and practical standpoints. In chart 8 the behavior of some twenty-five animals to an insulin dosage of  $\frac{1}{4}$  of a unit per kilogram over a period of twenty months is shown graphically. During this period the animals were used in the ordinary course of the research and were subjected to various doses of different samples of insulin as the occasion demanded. All of the control samples for the several months studied and all of the samples one-half an hour after dosage with  $\frac{1}{4}$  of a unit of insulin were assembled and the mean relative changes determined for the months which are indicated. These results were then compared with the grand mean relative change for this dosage (35 per cent,  $\pm 0.4$ ). This comparison is shown in chart 8. In only one of the months for which averages were determined did the results differ from the standard

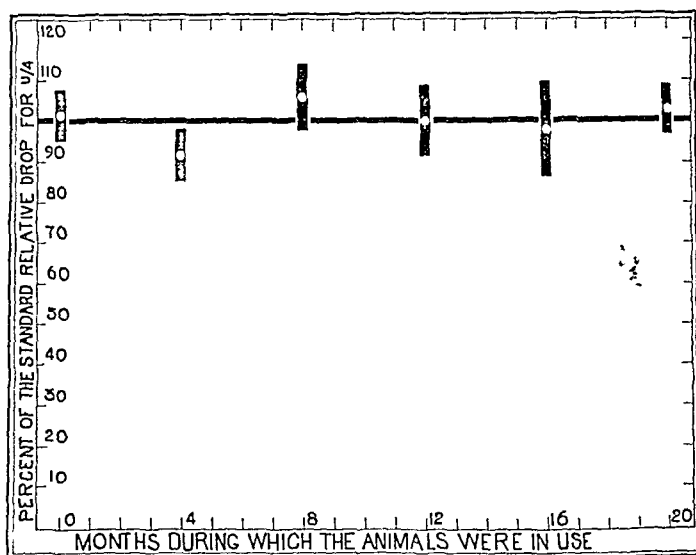


Chart 8—A chart to illustrate the bearing of insulin dosage on the response of the animal to subsequent dosage with insulin. The data are established from a group of animals which were in use in the research for twenty or more months. The points were determined as described in the text and are plotted for every fourth month. Although during this time the animals were subjected to various dosages, the response to  $\frac{1}{4}$  of a unit per kilogram is alone considered in the chart. This dose was selected for study because it was used most frequently and consequently more data were available. A study of the other doses which were used convinced us that they would have confirmed the data obtained from the  $\frac{1}{4}$  unit. The points in this chart were established from fifteen to twenty observations each. See the text for the interpretation of the chart.

relative drop by more than its mean deviation and even for this month the deviation was only slightly greater than the standard. So we find that in the only group available for this study there was rather less variation than would be expected on the basis of statistical theory. In

addition to the relatively small deviations that we find, there is a complete absence of any indication of trend, either toward a greater or a lesser sensitivity

Our work, then, is evidence in favor of the entire independence of consecutive doses of insulin so long as they are separated by an interval of at least a week. We have no evidence as to what would happen if the insulin were administered at shorter intervals, or if given for longer periods of time

#### THE BEARING OF THE CONCENTRATION OF THE INJECTED INSULIN SOLUTION ON THE RESPONSE OF THE SUBJECT

So far it has proved to be necessary to administer insulin by injection. This makes it necessary that the insulin be administered in solution, and so the question immediately arises as to the effect of the concentration of this solution on the apparent response of the subject. The effects that may arise from this cause may be either local or general. In any case they probably would be associated with absorption phenomena. It would hardly seem probable that any significant difference in behavior would result from variations in total osmotic pressure of the injected solution. The insulin is dissolved in isotonic salt solution and of itself constitutes so small a portion of the total molecular concentration, even in extreme doses, that changes in its concentration would not cause appreciable variations in the total osmotic strength.

The general problem has received theoretical attention on the part of several investigators. In fact, it would appear that its importance has been somewhat overemphasized in some cases, when one considers that, so far, there does not seem to be any satisfactory experimental evidence that, within the limits of ordinary practical necessity, there is any difference in the general effects of a given dose of insulin, whether it is administered in a concentrated or a dilute solution. It is obvious that when the dose is to be varied, either the concentration or the volume of the solution must be varied for a subject of a given weight. On theoretical grounds alone it seems quite as logical to expect variations in the effect when the volume of the injected solution is varied as it is to expect them when the concentration is changed. In the absence of direct experimental evidence which would tend to indicate that either method is unsatisfactory, it seemed to be justifiable to select the system that would prove to be the most simple in its technical use. We have, accordingly, varied the volume of the injected solution only with the weight of the subjects, 1 cc being injected for each kilogram of body weight. The concentration, on the contrary, has been varied with the selected dose, each cubic centimeter containing the dosage designated for each kilogram of body weight.

We have been able to find no evidence in our results that this method is in any way inferior to the other or that the results obtained by the two methods do not fully agree. It is only fair, however, to state that we have designed no experiments specifically to test this point.

#### THE SIGNIFICANCE OF LIGHT DOSAGE

A few papers have appeared in which the use of light dosage in insulin assay is specifically attacked. The general tendency in practice seems, either tacitly or explicitly, to favor the use of fairly heavy dosage.

Since we, on the contrary, are favoring the use of comparatively light doses, it will not be out of place to discuss the significance of a few of the objections that have been raised against this practice.

Occasionally the statement has been made that light doses have no effect or that there is an "all or none behavior." It seems to us that all of our evidence is against this point of view, in whatever form it may be expressed. Against the statement that light doses have no effect we offer the evidence of our own data, as shown in charts 5 and 6, which cover the range of dosage that apparently is meant in such statements. Extrapolation would indicate that with a dosage of  $\frac{1}{32}$  of a unit there should be a drop of approximately 10 per cent of the initial value. This is just outside the limits of precision of the methods that we have used for our blood sugar determinations, and so should be indicated if an appropriate series of observations were made. Such a series we do not have, but in a very short series of observations on rabbits the drop is 11 per cent of the initial. Miss Hrubetz, working in our laboratory, has unpublished data for the rat, which include a series of one hundred observations at this dosage. The relative blood sugar change for this dosage takes its proper place on a curve extrapolated from the results obtained from doses of  $\frac{1}{16}$ ,  $\frac{1}{8}$  and  $\frac{1}{4}$  of a unit per kilogram. Extrapolations beyond  $\frac{1}{32}$  of a unit indicate a percentage drop of such small magnitude as to be within the experimental error of the methods that are available, and so are at present incapable of experimental justification.

Moreover, on purely theoretical grounds, it is probable that extensive extrapolation is not justified. It has been shown that the proportionality of the curve falls off in its upper reaches, and that at least one reason for this lies in the fact that at the time when the samples were drawn the rate of change in the blood sugar concentration had not yet reached its maximum. While the precision of our sugar methods does not at present permit a critical study at the other end of the dose scale, the time curves shown in charts 1 and 2 would lead one to expect that the curves for extremely low doses would already be well on their way back toward the initial value at the time at which the samples were

drawn. This would lead to a flattening of the curve at this end as well, so that while direct extrapolation would indicate that a dose slightly less than  $\frac{1}{128}$  of a unit per kilogram would have no effect on the blood sugar level, it is probable we would actually find that only a zero dose would have zero effect.

We are hardly justified in basing a positive theoretical discussion on such an extensive extrapolation as is necessary here, in any case, much less so when the theoretical probability is that the shape of the curve would change in the region of the extrapolation. The failure of our technic to demonstrate the extremely small changes in blood sugar level which are to be expected to result from very small doses of insulin can

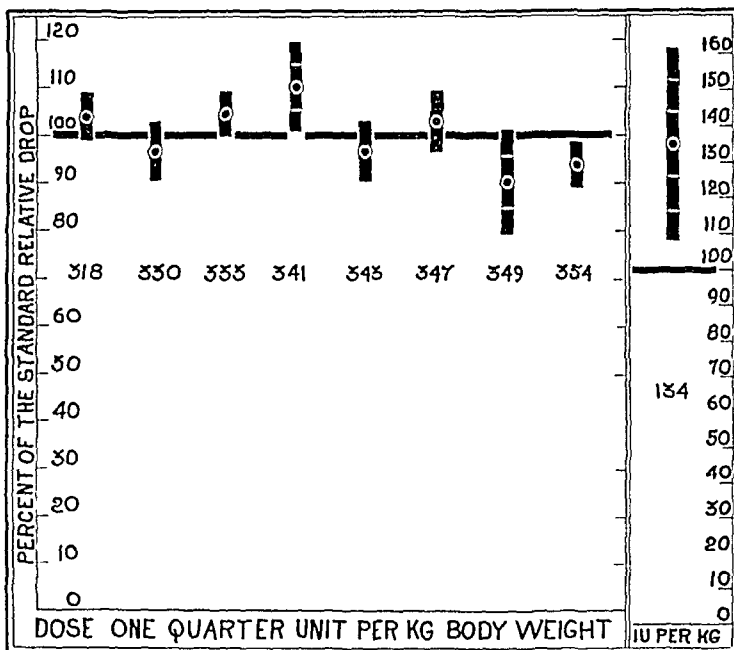


Chart 9—Individual response to insulin. In each case the points represent the degree of response of the individual as compared to the standard response taken from chart 6. The positions of these points were located as were those of chart 8. The vertical bars measure the precision with which the points were established and represent the indicated even multiples. The points were established from twenty to thirty observations each.

hardly be interpreted as indicating that they do not exist. As insulin continues to have the expected effect as far down the curve as it can be followed technically, it is difficult to justify assumptions that it acts differently beyond this point. We are, therefore, unable to interpret our data as giving any support to the hypothesis that light doses of insulin have no effect or that insulin in any manner acts according to an "all or none" principle.

## INDIVIDUALITY IN INSULIN RESPONSE

The possibility of idiosyncrasy must be borne in mind continuously in all physiologic work. Particularly in work of a quantitative nature, such as the present study, it is important to assure ourselves that our conclusions are not biased by the inclusion within the group of certain subjects that are distinctly more or less sensitive than is characteristic for the species. Unless it has been shown that such individuals do not exist, care must be exercised so to plan a research that the possible presence of variant individuals cannot bias the final results to a significant degree.

In our own work the presence of such variants was assumed, and we sought to avoid bias by using a considerable number of subjects in each of our groups, with the hope that bias would be eliminated statistically.

During the course of the work a sufficient number of similar observations were made on a few individuals to enable us to form some judgment of the sensitivity of these individuals. The results of this study are shown in chart 9. They clearly indicate not only that the animals do vary among themselves in their sensitivity to insulin, but that in an occasional animal this variation may be considerable and that it may be in either direction. So that unless the possibility of the presence of variants is considered, it may be a real menace to the reliability of results. From the fact that both hyposensitive and hypersensitive animals are shown to exist, it should be possible to eliminate bias by the use of a number of subjects.

## SUMMARY

1 When the dose is measured in units per kilogram of body weight and the blood samples are drawn thirty minutes after the injection of insulin, the relative drop in blood sugar is proportional to the logarithm of the dose through a considerable portion of the practical dose range.

2 It is impractical to use doses of less than  $\frac{1}{16}$  of a unit per kilogram because of the lack of sufficient precision in blood sugar methods, and of greater than  $\frac{1}{2}$  of a unit per kilogram because of the loss of proportionality for doses greater than this, when the samples are taken under the conditions which we have described.

3 The dietary regimen may influence the initial blood sugar concentration and, secondarily, the absolute concentration after insulin. We were unable to demonstrate that the quantity or the nature of the food in any way affected the relative blood sugar changes after insulin.

4 There is a direct relation between the body weight and sensitivity to insulin dosage when the effect of the insulin is compared with the

logarithm of the dose, so that when the dosage is measured in terms of units per kilogram of body weight, the same results are obtained with adult rabbits of widely varying body weights as are obtained when the animals are selected to a given constant weight

5 If insulin is not administered oftener than once a week nor for a longer period than twenty months, we have found no evidence that the response to subsequent dosage with insulin is in any way affected

6 There is no evidence that extremely light doses do not have the full expected effect. Appearances to the contrary may as well be due to technical failure as to absence of response

7 There is evidence that individual animals may be either hyposensitive or hypersensitive to insulin when their response is compared with the average response of a considerable group of animals

# PERNICIOUS ANEMIA

TREATMENT WITH EQUINE LIVER EXTRACT INJECTABLE EITHER  
SUBCUTANEOUSLY OR INTRAVENOUSLY

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AND

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In view of the obvious advantages of an injectable antipernicious anemia substance and the promising results reported by Gansslen,<sup>1</sup> Selander,<sup>2</sup> van Leeuwen,<sup>3</sup> Strauss, Taylor and Castle<sup>4</sup> and others with intravenous and intramuscular materials, this work was undertaken with the twofold objective of producing an improved injectable material that would be (a) of a definitely standardized potency and (b) of a chemical refinement sufficiently great to remove the irritating and objectionable elements and thus permit safer, more convenient and painless subcutaneous use

In order to begin with material of highest known potency, we used equine liver prepared as reported in our previous work<sup>5</sup> This method was essentially similar to that of Strauss, Taylor and Castle<sup>4</sup> Absolute alcohol sufficient to bring the liquid up to 95 per cent was added to the liver extract After standing, the precipitate was separated and dissolved in a convenient amount of water, and a phosphate buffer mixture was added in order to make the solution isotonic and to adjust the  $p_H$  of the finished product to 7.2 The potency of the extract was then standardized so that 1 cc was equivalent to 10 Gm of whole liver, to which 0.4 per cent of cresol was added as a preservative The solution was then filtered and sealed in ampules

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This work was done by a grant from the Chappel Foundation for Organotherapeutic Research at Northwestern University and Cook County Hospital

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2 Selander, P Injectable Liver Preparation, Hygiene 93 625, 1931

3 van Leeuwen, H C Treatment of Pernicious Anemia by Intravenous Administration of Liver Extract, Nederl tijdschr v geneesk 75 4425, 1931

4 Strauss, M B, Taylor, F H L, and Castle, W B Intramuscular Use of Liver Extract, J A M A 97 313 (Aug 1) 1931

5 Richter, Oscar, Meyer, A E, and Ivy, A C The Treatment of Pernicious Anemia with Horse Liver Extract, Preliminary Report, J A M A 98 1623 (May 7) 1932

Preliminary animal and laboratory tests were made to establish the safety of this material for parenteral administration. It was cultured for sterility, the absence of anaphylactic effects was shown on guinea-pigs, irritating qualities were found to be absent by subcutaneous and intramuscular injections into man, rabbits and dogs, rabbits were given injections of large doses at intervals without producing objective

TABLE 1—*Responses of Ten Patients with Pernicious Anemia to Subcutaneous and Intravenous Injections of an Equine Liver Extract*

Case	Age	Relapse	Days on Treatment	Maximum Reticulocyte, Percentage	Changes in Hemoglobin, Percentage		Changes in Red Blood Cells, Millions		Total Dosage, Cc	Injection Route	Comment
					Before	After	Before	After			
A B <sub>1</sub>	51	1	58	25.2	25	80	0.830	4.31	110.0	Subcutaneous	Patient also had a bleeding cervical polyp removed while on treatment
M C	60	2	48	27.6	24	83	0.840	4.17	91.0	Intravenous, 3 cc	Total of 57 cc, continued subcutaneously, 2 cc daily
M J	72	1	72	29.4	26	81	0.890	4.14	128.0	Subcutaneous	Marked psychosis, improvement
L K	68	3	57	5.0*	41	81	1.08	4.14	73.5	Intravenous	2.75 cc daily
A K	70	2	41	36.2	21	82	0.780	4.05	82.0	Subcutaneous	Marked mental improvement
J M	69	1	32	22.4	33	81	1.41	4.05	64.0	Subcutaneous	Marked mental improvement
P L	29	2	46	12.4*	47	94	1.75	4.59	40.0	Intravenous	From 2.5 to 3.5 cc on alternate days
A P	32	1	42	27.2	32	61	1.47	3.31	76.0	Subcutaneous	Still on treatment
M G	65	1	9	22.6	34	38	1.13	1.56	18.0	Subcutaneous	Still on treatment
N L	24	1	10	47.2	17	33	0.750	1.30	24.0	Subcutaneous	Entered moribund, unable to get suitable donor, still on treatment
Total				415	300	714	10.930	35.62			
Average Patient				41.5	30	71.4	1.09	3.56			
Average Net Gain					41.4		2.47				
Average Daily Gain					0.99+		59,000		1.6 cc	Average daily dose	

\* Three reticulocyte responses omitted from the average were atypical owing to other treatment given a short time prior to the beginning of this treatment.

effects, the vasodepressor action was measured by blood pressure assay on dogs, the results showing that 2 cc has a depressor action equivalent to that of 0.01 mg of histamine, which means that 2 cc of this material may be given subcutaneously or intravenously slowly without causing a significant histamine-like fall in blood pressure.

Through the courtesy of the attending staff of Cook County Hospital, thirteen patients with pernicious anemia were placed on treatment with this material. Daily reticulocyte counts and complete blood counts at five day intervals were made. The results are summarized in table 1.



It should be noted that in three of these cases (P L, L K and A B) our treatment had been closely preceded by other treatment, which had absorbed the peak of the reticulocyte response

In each of these cases several days were allowed to elapse after the prior treatment before beginning our injections, to permit the reticulocyte percentages to return to a low level. Although a secondary reticulocyte increase was observed as recorded, a typical response was not to be expected

Omitting these three cases, the average reticulocyte increase for the group was 30.15 per cent

The average daily gains in hemoglobin percentage and increase of erythrocytes amounted to 59,000 red blood cells and 0.99 per cent hemoglobin, which was greater than the results obtained by oral administration of the extract. A complete return to the normal blood picture was induced in from six to eight weeks

The previous history in the case of L K had a distinct bearing on this subject. The patient entered the hospital some months previously with 73 per cent hemoglobin and 3,200,000 red blood cells. She remained in the hospital for thirty days, during which time she was given orally large doses (equivalent to 720 Gm daily of whole liver) of a standard council-accepted cattle liver extract, and made very slight progress, a daily gain in hemoglobin of 0.19 per cent and of red blood cells, less than 7,000. After several months she reentered the hospital, with a low blood count, 41 per cent hemoglobin and 1,080,000 red cells, and the injection treatment, as shown in table 1, was started. Her response to this treatment averaged a daily gain of 0.53 per cent hemoglobin and 53,800 red blood cells, leading to a complete remission in fifty-six days

It is interesting to note that one patient (J Mc) had a chronic fibroid tuberculosis of four years' duration which was apparently arrested on entrance to the hospital. During the course of treatment, an acute process developed, which was diagnosed clinically tuberculous bronchopneumonia, and the patient had a septic temperature. In spite of the septic condition, he showed the usual reticulocyte response to parenteral liver therapy, but the red cell count has not risen above 3,200,000 in the past seven months, during which the patient has been receiving treatment

Comparison was made of the degree of chemical refinement attained in the various liver extracts available for hypodermic injection. The solid residue per hundred grams of fresh liver represented in the various materials was found to be in (a) our material, 0.405 Gm, (b) product A, 1.799 Gm, and (c) product B, 1.05 Gm

Thus each gram of total solids contained in our extract represents 246 Gm of liver, compared to 55 Gm of liver per gram of solids in product A and 95.2 Gm of liver per gram of solids in product B.

This comparative freedom from extraneous material is probably responsible for the nonirritating properties of the extract, and permits doses from three to four times greater with correspondingly longer intervals between.

The patients received dosages varying from 2 to 3 cc subcutaneously or intravenously, some daily and others on alternate days, the

TABLE 2—*Responses of Patients with Atypical Pernicious Anemia with Severe Complications to Subcutaneous Injections of Equine Liver Extract*

Case	Age	Relapse	Days on Treatment	Maximum Reticulocyte, Percentage	Changes in Hemoglobin, Percentage		Changes in Red Blood Cells, Millions		Total Dosage, Cc	Injection Route	Comment
					Before	After	Before	After			
A B	40	2	77	52*	27	81	0.870	4.06	144	Subcutaneous	Also had syphilis, antisyphilitic treatment 2 years prior to present relapse
R Br	59	1	26	1*	57	76	2.86	3.95	48	Subcutaneous	Was on Chappel's oral liver extract prior to present therapy, had reticulocyte count 17.4 per cent, also had infected knee joint, 200 cc of pus aspirated
J Mc D	63	1	73	27.2	17	54	0.710	3.26	170	Subcutaneous	Tuberculosis and bronchopneumonia while on treatment, followed by active tuberculosis of lungs throughout treatment
Totals			176		101	211	4.44	11.27			
Average			58		33	70	1.48	3.75			
Average Net Gain						37		2.27			
Average Daily Gain						0.637		39,000			

\* Three reticulocyte responses omitted from the average were atypical owing to other treatment given a short time prior to the beginning of this treatment.

average daily dosage being 1.5 cc. The subcutaneous injection of 2 or 3 cc caused the patient no more distress than the ordinary hypodermic injections of drugs in common use. A local sensation of warmth was reported that lasted for one or two hours.

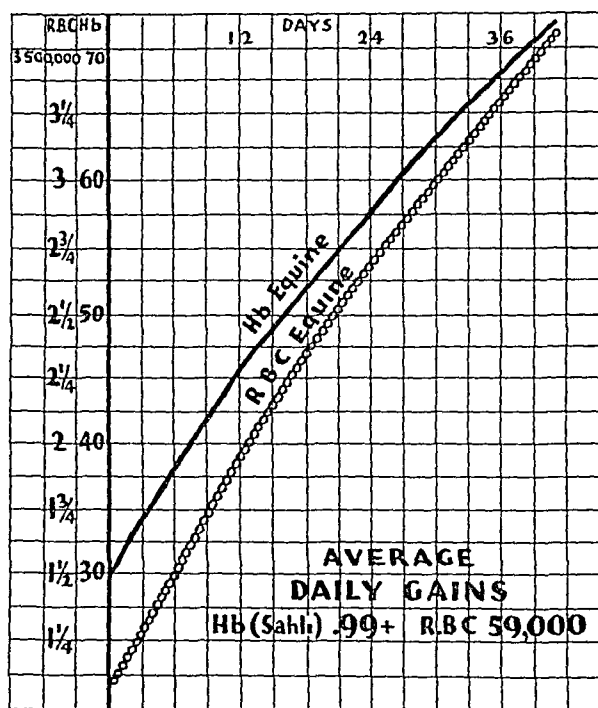
No other evidence of local or systemic reaction has been observed, objectively or subjectively with the subcutaneous treatments. This permitted routine administration by assistants or nurses.

On rapid intravenous injections into patients whose counts were below 1,000,000 red blood cells at a speed greater than 1 cc per minute, an immediate drop in blood pressure was noticed, manifested clinically by a rapid and weak pulse. This returned to normal within a few seconds, with no further reaction. The patients reported a feel-

ing of generalized warmth and well-being a few minutes after the injections, which persisted for several hours

In our experience with the series of patients receiving intravenous injections, no severe immediate or latent reactions were observed. A maximal and sufficient amount for each intravenous injection, we believe, should not exceed 3 cc, and injections should not be given at a rate faster than 1 cc per minute.

The peak of the reticulocyte response was reached somewhat sooner than by oral administration between the fourth and seventh days.



The course of progress made by ten patients with typical pernicious anemia who were given injections of equine liver extract

Other investigators have also reported earlier responses after intramuscular or intravenous injections of liver extract<sup>4</sup>

The sustained rate of gain for the red count and hemoglobin was found to be faster with the injectable material, leading to an earlier complete hematologic remission.

As previously reported, a usable injectable material has a number of advantages over oral extracts, particularly in the following cases: for patients with an aversion to liver, for those who are vomiting or are unable to assimilate orally, because of gastro-intestinal dysfunction for stuporous or comatose patients, and for uncooperative patients etc.

In addition, owing to the bland and harmless nature of our extract, it can be used subcutaneously as a routine treatment. Patients do not

object to this painless injection. Patients on maintenance, returning to our clinic, receive injections at intervals and are not subjected to dietary requirements.

For maintenance use, the interval between injections varies with different patients and with complications that may arise from time to time in the same patient. For this reason we have insisted that all patients return to the clinic periodically for a complete blood count to establish the individual intervals of dosage.

#### CONCLUSIONS

1. An injectable equine liver extract was found to be capable of producing a complete remission in cases of pernicious anemia within from six to eight weeks.

2. This extract was found to be comparatively painless on subcutaneous administration, and was safe when the precautions indicated for intravenous use were observed.

# UREA CLEARANCE TEST AS AN INDEX OF RENAL FUNCTION

## III STUDIES OF PATIENTS WITH BRIGHT'S DISEASE

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The material for this study is a series of ninety-four observations of the urea clearance in twenty-one cases of Bright's disease. Ten ward patients and eleven dispensary and office patients are included, the data for the latter group are of importance in the determination of the value of the urea clearance test in the ambulatory subject. The other ten patients were investigated while at complete rest in bed in the wards of the New York Post-Graduate Hospital.

Our observations covered a period of ten months. One case of acute diffuse glomerular nephritis, fifteen cases of chronic diffuse glomerular nephritis and five cases of vascular or arteriosclerotic nephritis were investigated. In two cases of chronic diffuse glomerular nephritis, while the patients were under observation, a definite so-called nephrotic component developed, as shown by increasing edema, a high amount of blood cholesterol, marked proteinuria and a low protein content and an inverted albumin-globulin ratio in the blood serum. Space does not permit the publication of a careful clinical analysis of every case investigated. Only a few will be presented in detail and the urea clearance will be correlated with the main clinical findings of all the cases in the tables.

### PROCEDURE

The procedure described by Moller, McIntosh and Van Slyke,<sup>1</sup> as outlined in our first paper,<sup>2</sup> was followed throughout this investigation. Breakfast, but without coffee, was allowed each patient on the morning of the test. The ambulatory patients were sitting down during the period when the samples of urine and blood

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From the Harriet Weil Memorial Fund, Department of Medicine, New York Post-Graduate Medical School and Hospital

1 Moller, E., McIntosh, J. F., and Van Slyke, D. D. Studies of Urea Excretion. II Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, *J. Clin. Investigation* 6: 427, 1928.

2 Brugger, M., and Mosenthal, H. O. The Urea Clearance Test as an Index of Renal Function. I Studies of Normal Subjects, *Arch. Int. Med.* 50: 351 (Sept.) 1932.

were collected. The ward patients were at complete rest in bed. All specimens were carefully collected and timed by one of us. The specimens of urine from patients in uremic coma were obtained by the catheter.

Urea in the blood and urine was determined by the gasometric urease method of Van Slyke.<sup>3</sup> The accessory chemical examination of the blood, as reported in table 1, was done according to the following methods: uric acid, Herman Brown,<sup>4</sup> creatinine, Folin and Wu,<sup>5</sup> cholesterol, Sackett,<sup>6</sup> total proteins, albumin and globulin, combined methods of Howe,<sup>7</sup> and carbon dioxide-combining power of the plasma, Van Slyke and Neill.<sup>8</sup> In table 1 the degree of edema and uremia and the urinary findings are expressed in plus sign grades.

## RESULTS

We have had occasion to study one case of acute diffuse glomerular nephritis (table 1, case 1). One week following an acute otitis media, the patient noticed that his urine was the color of "dark coffee" and he complained of a dull aching pain in the lower part of the back. He was admitted to the ward a short time later with the diagnosis of acute diffuse glomerular nephritis. He remained in the hospital for three weeks and was discharged apparently well. The results of chemical examination of the blood and of examination of the urine were normal on several occasions before the patient's discharge. On request, he returned to the dispensary two months later stating that he felt well. Examination of the urine at that time showed albumin, occasional red blood cells and hyaline as well as finely granular casts. The urea clearance showed about 88 per cent of renal function, a figure definitely within the normal range.

Van Slyke and his associates<sup>9</sup> have shown that in most instances of acute diffuse glomerular nephritis, the urea clearance falls to 50 per cent or less of normal during the first two months after the onset, and that the essential for a good prognosis is that within four months after the acute onset the clearance should gradually mount to a normal level.

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6 Sackett, G. E. Modification of Bloor's Method for Determination of Cholesterol in Whole Blood or Blood Serum, *J. Biol. Chem.* **64** 203, 1925.

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8 Van Slyke, D. D., and Neill, J. M. The Determination of Gases in the Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J. Biol. Chem.* **61** 523, 1924.

9 Van Slyke, D. D., Stillman, E., Moller, E., Ehrlich, W., McIntosh, J. F., Leiter, L., MacKay, E. M., Hannon, R. R., Moore, N. J., and Johnston, C. Observations on the Courses of Different Types of Bright's Disease and on the Resultant Changes in Renal Anatomy. *Medicine* **9** 257, 1930.

TABLE 1—Urea Clearance Studies in Cases of Bright's Disease

Case No.	Age	Date	Remarks	Edema	Anemia			Blood								Urine					Type of Renal Lesion																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														
					Blood Pressure	Red Blood Cells, Millions	Hemoglobin, per Cent	Uremia	Urea Nitrogen, Mgr per 100 Cc	Uric Acid, Mgr per 100 Cc	Creatinine, Mgr per 100 Cc	Total Proteins, Gm per 100 Cc	Albumin, Gm per 100 Cc	Globulin, Gm per 100 Cc	Co <sub>2</sub> Combining Power, per Cent in Vol	Cholesterol, Mgr per 100 Cc	Albumin	Red Blood Cells	White Blood Cells	Casts		Urea Clearance per Cent of Normal																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																													
1 L R 8	19	11/12/30	Acute diffuse glomerular nephritis 3 months ago following discharging ear	Lower eyelids	108/ 68	4.1	81	0																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																											</

3/20/31	Eliminating edema	++	144/100	0	46 0				+++	+	+	H + G +	13	nephritis "nephrotic component" secondary contracted kidney uremia
4/16/30	Discharged from hos- pital with small residual edema	+	138/76	72	0	28 0	5 3	2 6	416	6	+	H + G +	18	
6/30/31	Readmitted semi- comatose	++	210/130	45	++	117 0	5 9	15 0	71	3 4	8 0	H + G +		
7/ 3/31	Died													
6/17/30	Albuminuria dis- covered accident- ally 6 years ago	Eyelids	220/110	61	±	75 0	4 8	8 0	8 3	5 4	2 9	0		Chronic diffuse glomerular nephritis, secondary contracted kidney with pre uremic symptoms
6/19/31	Signed release Aug 8, 1931, feeling quite comfortable, blood pressure gradually fell to 150/95 but pre uremic symptoms (nausea and head- aches) continued				±	87 1						H + G ±	6 1	
9/ 9/30	Six months ago a protracted cold, 3 months later ankles began to swell, face swollen for past 2 weeks Vomiting, headache Died Dec 12, 1930	++	160/95	74	0	22 0	5 3		5 2	3 4	1 8			Chronic diffuse glomerular nephritis, secondary contracted kidney, uremia
3/12/31	History of headache and vomiting for past month	±	228/132	41	+	110 3	9 6	10 5				H + G ±		Secondary contracted kidney, uremia
3/20/31	Died March 31, 1931				++	167 0							4 4	
2/ 6/31	Admitted in uremic coma, indwelling catheter	+	234/160	69	++	147 0	12 2	13 4				H 0 G +	4 5	Secondary contracted kidney, uremia
2/ 8/31	Died													
4/ 6/31	Admitted April 5, 1931, in uremic coma	+		71	+	63 0	7 2	5 7				H ± G ±		Secondary contracted kidney, uremia
4/ 7/31					+	76 3						H ± G ±	5 6	
4/27/31	Died May 16, 1931	±		46	++	104 0						H ± G ±	7 0	



TABLE 1—Urea Clearance Studies in Cases of Bright's Disease—Continued

Case No	Age	Date	Remarks	Edema	Anemia			Blood										Urine				Type of Renal Lesion			
					Blood Pressure	Red Blood Cells, Millions	Hemoglobin per Cent	Urea Nitrogen, Mg per 100 Cc	Uric Acid, Mg per 100 Cc	Creatinine, Mg per 100 Cc	Total Proteins, Gm per 100 Cc	Albumin, Gm per 100 Cc	Globulin, Gm per 100 Cc	CO <sub>2</sub> Combining Power, per Cent in Vol	Cholesterol, Mg per 100 Cc	Albumin	Red Blood Cells	White Blood Cells	Casts	Urea Clearance, per Cent of Normal					
9 F 6	15	1/12/31	Twelve years ago albumin found in urine following influenza (ambulatory)	+	141/90	1.6	90	0	19.5									+	+	+	+	H	15	Chronic diffuse glomerular nephritis	
		2/16/31		+				0	19.7									+	+	+	+	H	12		
		4/20/31		+				0	24.9									+	+	+	+	H	42		
		6/25/31	Six weeks ago had cold with fever, ill in bed for 1 week	+		2.9	60	0	21.4									+	+	+	+	H	26		
10 F 13	15	2/25/31	In January, 1929, patient complained of edema of lower eyelids, vomiting and headaches (ambulatory)	+	156/104	5.04	81	0	21.4															Chronic diffuse glomerular nephritis	
11 D G 22	19	1/ 5/31	Acute diffuse glomerular nephritis following erysipema in March, 1930, edema of legs first noticed in June, 1930 (ambulatory)	+	186/130	3.32	66	0	11.7				4.6					+	+	+	+	H	35	Chronic diffuse glomerular nephritis	
		2/ 6/31		+	220/140			0	15.5									500	+	+	+	+	H	32	
		3/17/31		+	174/112	3.3	68	0	31.8	4.9								379.8	+	+	+	+	H	24	
		4/14/31		+		3.5	70	0	27.9	5.5								400	+	+	+	+	H	34	
		5/26/31		+	174/120			0	41.6										406	+	+	+	+	H	30

12 H R 10	25	12/22/30	Edema of legs and lower eyelids first noticed in 1925 (ambulatory)	±	164/122	0	35 4	1 17	375	++	±	±	H ±± G	23	Chronic diffuse glomerular nephritis
		2/12/31		±	154/104	0	35 3		483 3	++	±	±	H ±± G	23	
		4/21/31		±	142/100	0	33 4		315 8	++	±	±	H ±± G	26	
		6/11/31		±		0	45 5			++	±	±	H ±± G	18	
13 L W 2	31	12/18/30	Albuminuria discovered accidentally in 1927, urine has always contained albumin and casts since then (ambulatory)	0	122/ 74	0	17 4	5 0	200	+	±	±	H ±± G	101	Chronic diffuse glomerular nephritis
14 R N 7	41	1/17/31	Four years ago left nephrectomy for lithiasis (ambulatory)	±	140/ 85	4 84	31 7	1 3		±	±	±	H ±± G	11	Chronic diffuse glomerular nephritis
		4/17/31		±	130/ 80		33 8		272 2	+	±	±	H ±± G	25	
15 L S 16	47	3/23/31	In March, 1923, attacks of vertigo and headaches, high blood pressure discovered then (ambulatory)	0	206/174	0	16 9			±	±	±	H ±± G	71	Arterio sclerotic nephritis
		5/25/31		0		0	15 5			±	±	±	H ±± G	92	
16 F M 20	53	6/15/31	Diabetes for 5 years	0	186/116	0	27 0			+	±	±	H ±± G	45	Arterio sclerotic nephritis

In a case of chronic diffuse glomerular nephritis (table 1, case 13) albuminuria and cylindruria were present continuously for the four years prior to examination with no diminution in the clearance value below the normal figures. Case 15 (table 1) illustrates the same point. It follows that there may be distinct signs indicative of a pathologic condition of the kidneys, as revealed by examination of the urine, while the urea clearance values maintain a normal level. In a large number of these cases, other tests or indexes of renal function are also normal. Recently, Wakefield, Power and Keith<sup>10</sup> have observed that there may be definite signs of renal disease even when all the tests of renal function that they employed are within the limits of normal variations.

TABLE 2—*Difficulty in Obtaining Checks with the Urea Clearance in Patients with Bladder Retention*

Case No	Age	Type of Renal Lesion	Remarks	Blood Urea Nitro gen, Mg per 100 Cc	Urine Urea Nitro gen, Mg per 100 Cc	V <sub>c</sub>	$\sqrt{V}$	Blood Cleared of Urea, Cc per Minute	Urea Clearance, per Cent of Normal	$\frac{U}{B}$
1 J C 19	58	Arterio sclerotic nephritis		16.1	322.6	2.83		36.6	75	20.0
					305.6	2.02		38.3	51	19.0
				29.2	566.8	2.21		42.8	57	19.4
2 M K 17	54	Arterio sclerotic nephritis	500 to 1,000 cc of water by mouth necessary to obtain two hourly specimens	26.9	536.0	0.25	0.50	9.9	18	19.9
					485.8	3.36		60.8	81	18.1
				22.6	440.1	0.59	0.77	15.0	28	19.5
3 B F W 4	58	Arterio sclerotic nephritis	Voluntary control of bladder partially lost following cerebral hemorrhage three years ago	10.7	722.4	0.28	0.53	35.9	67	67.5
					926.6	0.02	0.15	13.1	24	86.6

This period in the development of chronic diffuse glomerular nephritis, that is when there are albuminuria and a perfectly normal capacity of the kidney to eliminate both fluids and solids, has been called the compensated stage. Little by little, sometimes very slowly, sometimes fairly rapidly, renal function becomes progressively diminished. When this has taken place the stage of decompensation has set in. The borderline between the compensated and decompensated stage cannot be definitely defined. The gradual failure of the kidney to act with a normal degree of efficiency is the result of the formation of connective tissue and a replacement thereby of active renal parenchyma. When

<sup>10</sup> Wakefield, E. G., Power, M. H., and Keith, N. M. Inorganic Sulphates in the Serum in Early Renal Insufficiency, *J. A. M. A.* 97:913 (Sept. 26) 1931.

this process has advanced, as signalized by marked diminution in renal function, the so-called secondary contracted kidney presumably has developed

Clearances consistently under 50 per cent of normal were taken as definite evidence of functional impairment of the kidney. In most of our cases of chronic diffuse glomerular nephritis (table 1, cases 2 to 14) the clearance was well below 50 per cent of normal. The urea clearance in these patients may be consistently at the same low level for months and then gradually decrease to threatening levels. In other cases, the advent of some intercurrent infection produced a sudden drop in the clearance. Case 9 (table 1) illustrates the latter point well.

Our studies of the urea clearance in Bright's disease bear out the clinical observation that patients with chronic diffuse glomerular nephritis rarely show marked improvement in the functional capacity of the kidneys irrespective of the therapeutic measures employed. This holds true when the diminution in renal function is caused by the formation of connective tissue and the obliteration of some of the renal elements. Transient occurrences that depress renal activity, notably intercurrent acute infections, as mentioned in the preceding paragraph, acute exacerbations of the nephritis or passive congestion, all of which may have a self-limited course or may be set aside by treatment, will produce temporary embarrassment of renal function, as shown by various tests, including the urea clearance. However, after such episodes have run their course, the kidney resumes its ability to functionate, and the various tests for renal function improve and assume the level at which they were before the complication occurred.

Some of our patients have maintained themselves comfortably with extremely low clearances. The patient in case 3 (table 1), studied in the wards, showed clearances ranging from 12 per cent to 18 per cent of normal and asked to be discharged because he felt fairly well. He left the hospital, but was readmitted four months later in uremic coma and died within four days. Another patient (table 1, case 4) complained of occasional vomiting and headache. There was marked retention of urea, uric acid and creatinine, and the urea clearance at that time was 61 per cent of normal. He signed his release from the wards two weeks later stating that he felt much more comfortable (the blood pressure had fallen from 220 systolic and 110 diastolic to 150 systolic and 90 diastolic), but occasional vomiting and headache continued. We have not heard from the patient since.

Our observations in terminal cases of glomerular nephritis agree with those of Van Slyke and his associates.<sup>9</sup> When the clearance values fall to about 5 per cent of normal, uremia is impending. We have not

observed any patients with less than 5 per cent of normal clearance who lived for more than two weeks

The elimination or deposition of large amounts of nephritic edema seems to have little effect on the urea clearance. Case 2 (table 1) was first observed as an ambulatory case, with the clinical diagnosis of chronic diffuse glomerular nephritis, added to which was a definite nephrotic component. The clearances at monthly intervals were 26, 40 and 30 per cent of normal, respectively. During this time, the edema gradually increased until it extended well up the small of the back. The patient was hospitalized for several weeks, and the edema disappeared almost completely. During his stay in the hospital, the clearances were 39 per cent and 29 per cent of normal on two separate occasions. For the three months preceding the writing of this report, he has again been studied as an ambulatory patient, the clearances practically remaining the same. Case 3 (table 1) illustrates the same point. The water balance of the sufferer with Bright's disease, therefore, often does not affect urea clearances.

Case 2 (table 1) serves to illustrate another point. In our first paper,<sup>2</sup> we demonstrated that moderate exercise increases the urea clearance in normal subjects. When the kidney becomes functionally impaired, however, moderate activity, such as walking, is apparently without material influence on the blood urea clearance.

In five cases of vascular or arteriosclerotic nephritis, we have been able to obtain only three satisfactory studies of clearance. We have found that the elderly patient often finds it difficult to empty the bladder completely, and that satisfactory studies of clearance cannot be made even if large amounts of water are given before and during the test. Cases 1, 2 and 3 (table 2) demonstrate the difficulty in obtaining checks for the two hours studied on the same day. Van Slyke and his collaborators,<sup>11</sup> in a later paper, have shown that the simple  $U/B$  ratio (when  $U$  signifies the concentration of urea in the urine and  $B$  the concentration of urea in the blood), without taking into account the volume of urine as determined for standard and maximum clearances, closely approximates the clearance values when the secretion of urine is less than 2 cc per minute. It is often difficult, however, to gage the amount of retention and to be reasonably certain that the secretion of urine is less than 2 cc per minute. In these instances, we have determined the  $U/B$  ratio, and although these values have been checked rather closely in some cases, we have been somewhat hesitant to include the

11 Van Slyke, D. D., McIntosh, J. F., Moller, E., Hannon, R. R., and Johnston, C. Studies of Urea Excretion. VI. Comparison of the Blood Urea Clearance with Certain Other Measures of Renal Function, *J. Clin. Investigation* 8: 357, 1930.

results in the general series Case 2 (table 2) required the administration of large amounts of water before and throughout the test merely to insure the passage of two samples of urine in two hours

We have studied a number of patients with Bright's disease (not included in the series) in whom clearance studies showed values between 55 per cent and 70 per cent of normal—figures that we consider in the doubtful range It is probable, as Addis<sup>12</sup> has shown, that the occasional patient showing a somewhat lower clearance than the average normal may have no impairment of renal function As the clearance falls, the odds that any given patient has no impairment of renal function are, of course, increased In such cases, it is advisable, and indeed necessary, to consider all the clinical data as well as other tests for renal function before a definite conclusion is reached

#### COMMENT

Addis<sup>12</sup> has maintained that the elimination of urea by the kidney is proportional to the blood urea content and the amount of renal secreting tissue He assumed, therefore, that any factor expressing the relationship between the output of urea and the urea content of the blood (under standard conditions of urine excretion) is indicative of the amount of secreting tissue in the kidney The urea clearance test of Moller, McIntosh and Van Slyke<sup>1</sup> is an expression of this relationship The problem of renal function, however, is not the problem of urea excretion alone We would rather believe that the activity of the kidney is composed of different functions, which to a certain degree act independently of one another

The elimination of urea is an important excretory function of the kidney, and it is often the first to become affected in Bright's disease In these instances, urea clearance tests may imply some impairment of renal function, while other functional tests prove to be negative Derangement of kidney function in the early stages of Bright's disease, however, is not always demonstrated by excretion of urea We shall be able to show later that the occasional case may present itself with a definite degree of retention of uric acid in the blood (in the absence of a gouty diathesis) or with a diminished ability of the kidney to concentrate the urine, in the presence of normal clearance values Recently, Wakefield, Power and Keith<sup>10</sup> have observed cases of Bright's disease with retention of inorganic sulphates in the serum and normal clearance values Obviously, the complexity of normal renal activity is reflected in its functional pathology It seems imperative, therefore, especially in the early stages of Bright's disease, to determine the efficiency of the

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12 Addis, T Renal Function and the Amount of Functioning Tissue, Arch Int Med 30 378 (Sept) 1922

kidneys from all possible angles before any conclusions are reached as to the presence or absence of functional impairment

The urea-excreting ability of the kidney, expressed as the urea clearance, nevertheless, is a valuable clinical adjunct in the study of renal function. In many instances, when observed at regular intervals over a period of time, clearance values indicate the clinical progress of the case and may be of definite prognostic significance.

One can infer from the data obtained in a large series of normal subjects<sup>13</sup> that patients with Bright's disease showing clearances above 75 per cent of normal probably have no impairment of renal function. This statement is made with a certain degree of reservation, since we have stressed the fact that this is not true in all cases. Values between 75 per cent and 50 per cent of normal should be considered in the doubtful range, because in view of some of the results obtained in normal subjects, it is evident that the urea clearance may be considerably lower than the average normal value with no decrease in renal efficiency. Values below 50 per cent always imply impairment of renal function. We agree with Van Slyke, Stillman and their co-workers<sup>9</sup> that in the chronic nephritides, clearance figures below 20 per cent may be considered as indicating the terminal stage of Bright's disease, although in some such cases months have elapsed before uremia has developed. Pre-uremic symptoms, such as nausea, vomiting and headache, are usually present when the clearance has fallen to 10 per cent of normal, but with values less than 5 per cent all the uremic manifestations are usually evident, and death occurs within a few days.

The urea clearance is in some instances little affected by the elimination or deposition of nephritic edema. This is of distinct advantage in any test of renal function. It is of equal value whether studied in the ambulatory or in the recumbent patient, provided there is definite renal insufficiency. With clearance values below 50 per cent of normal, moderate exercise, such as walking, apparently does not influence the amount of blood cleared of urea in a unit period of time.

In marked prostatic obstruction or incontinence from any cause, when it is impossible to gage even approximately the output of urine, clearance studies or the calculation of the  $U/B$  ratio cannot be satisfactorily made, unless catheterization is resorted to. The occasional contact with such cases and the accuracy required in collecting and timing the specimens of urine and in the determination of urea in the blood and urine detract somewhat from the use of this ratio as a routine measure in an active hospital service or in a physician's office.

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<sup>13</sup> Moller, McIntosh and Van Slyke (footnote 1) Bruger and Mosenthal (footnote 2) Goldring, W. Studies of the Kidney in Acute Infection, II Observations with the Urea Clearance Test in Acute Rheumatic Infection, *J. Clin. Investigation* **10** 345, 1931

## SUMMARY

Ninety-four observations of the urea clearance in twenty-one patients with Bright's disease are reported. The urea clearance test is shown to be a valuable clinical adjunct in the study of renal function. Clearance values above 75 per cent of normal usually, though not always, suggest no impairment of renal function. Values between 75 per cent and 50 per cent should be considered in the doubtful range, and other functional tests should be carried out before any conclusions are drawn as regards the status of renal function. Clearance figures below 50 per cent of normal always imply decreased renal efficiency. In cases of Bright's disease with definite impairment of renal function, moderate exercise is without any influence on the urea clearance. The elimination or deposition of nephritic edema is shown in some instances to have little effect on the blood urea clearance.



# UREA CLEARANCE TEST AS AN INDEX OF RENAL FUNCTION

## IV THE UREA CLEARANCE TEST IN RELATION TO OTHER TESTS AND MEASURES OF RENAL FUNCTION

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The urea clearance studies in twenty-one cases of Bright's disease, which formed the nucleus of the preceding paper in this series,<sup>1</sup> will be correlated in the following pages with various other tests and measures of renal function. Van Slyke, McIntosh, Moller, Hannon and Johnston<sup>2</sup> and Johnston<sup>3</sup> have compared the urea clearance with the concentrations of urea, uric acid, creatinine and hemoglobin in the blood, the excretion rate of phenolsulphonphthalein and the urea concentration ratio in nephritic subjects. Our work permits us to compare our findings concerning the blood urea clearance in subjects with Bright's disease with the concentrations of urea, uric acid and creatinine in the blood, the blood count (hemoglobin and red blood cell count), the two hour test for renal function and the urea concentration ratio

$$\frac{\text{urine urea concentration}}{\text{blood urea concentration}}$$

### METHODS

Urea in blood and urine was determined by the gasometric urease method of Van Slyke,<sup>4</sup> uric acid by the method of Herman Brown<sup>5</sup> and creatinine by the

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1 Brugger, Maurice, and Mosenthal, H O The Urea Clearance Test as an Index of Renal Function III Studies of Patients with Bright's Disease, Arch Int Med, this issue, p 544

2 Van Slyke, D D, McIntosh, J F, Moller, E, Hannon, R R, and Johnston, C Studies of Urea Excretion VI Comparison of the Blood Urea Clearance with Certain Other Measures of Renal Function, J Clin Investigation 8 357, 1930

3 Johnston, C The Relationship of Blood Uric Acid Content to the State of Renal Function in Nephritis, J Clin Investigation 9 555, 1931

4 Van Slyke, D D Determination of Urea by Gasometric Measurement of the Carbon Dioxide Formed by the Action of Urease, J Biol Chem 73 695, 1927

5 Brown, H The Determination of Uric Acid in the Blood, J Biol Chem 68 123, 1926

method of Folin and Wu,<sup>6</sup> hemoglobin readings were obtained with the Dare instrument, the red cell count was done in the usual way, and the two hour renal function test was carried out according to the procedure of Mosenthal.<sup>7</sup>

The table mentions all the cases studied, however, only a few of the tests carried out are reported in each instance, the results that are not charted confirmed those that are offered, and a presentation of them would lead to much unnecessary duplication. The constituents of the blood and the various tests for renal function studied cover all the ranges from normal values to figures obtained with maximal impairment of renal function.

#### THE UREA NITROGEN CONTENT OF THE BLOOD

MacKay and MacKay<sup>8</sup> and Moller, McIntosh and Van Slyke<sup>9</sup> have shown that more than half of the functioning tissue of the kidneys may be destroyed before the blood urea nitrogen rises above normal limits. The maximum normal blood urea nitrogen used as a basis for their conclusions was 23 mg per hundred cubic centimeters, obtained by MacKay and MacKay<sup>10</sup> in a study of 278 observations on 161 normal persons (presumably on their usual diet).

Mosenthal<sup>11</sup> and Addis and Watanabe<sup>12</sup> had previously shown that in normal persons the blood urea content varies more or less directly with the protein intake and these observations were further supported by MacKay and MacKay<sup>10</sup>. It appears incorrect to make comparisons between functional tests of the kidney and the blood urea content in patients with Bright's disease whose protein intake is usually restricted when the maximum normal urea content of the blood is taken from a series of normal subjects on their usual diet. From clinical observations

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6 Folin, O., and Wu, H. A System of Blood Analysis, *J Biol Chem* **38** 98, 1919

7 (a) Mosenthal, H. O. Renal Function as Measured by the Elimination of Fluids, Salt, Nitrogen and the Specific Gravity of the Urine, *Arch Int Med* **16** 733 (Nov) 1915, (b) Renal Function as Measured by the Elimination of Fluids, Salt, Nitrogen and the Specific Gravity of the Urine. II. The Effect of High, Low and Normal Diets, *Arch Int Med* **22** 770 (Dec) 1918

8 MacKay, E. M., and MacKay, L. L. The Relation Between the Blood Urea Concentration and the Amount of Functioning Renal Tissue, *J Clin Investigation* **4** 127, 1927

9 Moller, E., McIntosh, J. F., and Van Slyke, D. D. Studies of Urea Excretion. IV. Relationship Between Urine Volume and Rate of Urea Excretion by Patients with Bright's Disease, *J Clin Investigation* **6** 485, 1928

10 MacKay, E. M., and MacKay, L. L. The Concentration of Urea in the Blood of Normal Individuals, *J Clin Investigation* **4** 295, 1927

11 Mosenthal, H. O. Metabolism in Nephritis, in Barker, L. F., Hoskins, R. G., and Mosenthal, H. O. *Endocrinology and Metabolism*, New York, D Appleton and Company, 1922, vol 4, p 311

12 Addis, T., and Watanabe, C. K. The Causes of Variation in the Concentration of Urea in the Blood of Young Healthy Adults, *Arch Int Med* **19** 507 (April) 1917

in all types of cases, it seems to us that a blood urea nitrogen of more than 15 mg per hundred cubic centimeters on a protein intake of about 40 Gm per day suggests retention of urea. We have found (data to be published) that the average city dweller, left to his own dietetic initiative, consumes about 40 Gm of protein per day.

Whatever value of urea nitrogen in the blood is taken as an indication of retention of urea, there is no doubt that marked degrees of renal insufficiency may exist, as measured by the urea clearance test, while decidedly normal values for urea nitrogen are found in the blood. Case 11a (table) reveals a urea nitrogen of 11.7 mg per hundred cubic centimeters of blood with only 35 per cent of the average normal clearance. Our findings, in general, agree with those of MacKay and MacKay,<sup>8</sup> Moller, McIntosh and Van Slyke<sup>9</sup> and Van Slyke, McIntosh, Moller, Hannon and Johnston,<sup>2</sup> that normal values for urea nitrogen may be obtained in the blood of patients with Bright's disease who have lost as much as 60 per cent of their renal function, as measured by the urea clearance test. Inasmuch as we look on a urea nitrogen of more than 15 mg per hundred cubic centimeters of blood as suggestive evidence of urea retention in the blood of patients on a restricted protein intake, we cannot state definitely, as Van Slyke and his collaborators<sup>2</sup> have done, that the urea nitrogen of the blood does not become elevated until the clearance has fallen to 50 per cent of the average normal value. We have observed cases suggesting slight retention of urea in the blood with clearances somewhat above 50 per cent of normal.

#### THE URIC ACID CONTENT OF THE BLOOD

In the majority of cases of Bright's disease the uric acid is the first substance in the blood to become augmented with increased impairment of renal function. Chace and Myers,<sup>13</sup> Myers, Fine and Lough<sup>14</sup> and Baumann, Hansmann, Davis and Stevens<sup>15</sup> have shown that an increase in the uric acid content of the blood may be one of the earliest signs of renal insufficiency. The blood uric acid, however, is also increased in gout, leukemia, pneumonia, essential hypertension, pernicious anemia and several other conditions. Excluding such clinical entities in any case of Bright's disease, the uric acid content of the blood is significant. Uric acid, like urea, is largely of exogenous origin, and in any uncom-

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13 Chace, A. F., and Myers, V. C. The Value of Recent Laboratory Tests in the Diagnosis and Treatment of Nephritis, *J. A. M. A.* **67** 929 (Sept. 23) 1916.

14 Myers, V. C., Fine, M. S., and Lough, W. G. The Significance of the Uric Acid, Urea, and Creatinine of the Blood in Nephritis, *Arch. Int. Med.* **17** 570 (April) 1916.

15 Baumann, L., Hansmann, G. H., Davis, A. C., and Stevens, F. A. The Uric Acid Content of the Blood Compared with the Renal Dietary Test, *Arch. Int. Med.* **24** 70 (July) 1919.

plicated case of Bright's disease with a restricted protein intake, a uric acid content of 5 or 6 mg per hundred cubic centimeters of blood is certainly indicative of renal insufficiency

Recently, Johnston<sup>3</sup> compared the uric acid content of the blood with the urea clearance in thirty cases of renal disease. He concluded that the blood uric acid is of little value as an indicator of renal function, and he found that as much as 80 per cent of the urea excretory power of the kidney may be lost and normal values for uric acid still be found in the blood. Our results agree with those of Johnston<sup>3</sup> in this respect namely, that moderately increased blood uric acid (from 4 to 6 mg per hundred cubic centimeters of blood) may accompany either slight or maximal renal damage, but we have found in the large majority of cases with renal insufficiency, as measured by the blood urea clearance test, a definite increase in the uric acid content of the blood above the normal maximum of 4 mg per hundred cubic centimeters (table, cases 2b, 4, 10 and 11b)

We have also made the observation that the uric acid content of the blood may be slightly increased in cases of Bright's disease with no impairment of renal function as measured by the urea clearance. Case 13 (table) is an example. Our belief is that the uric acid may be increased in the blood as one of the earliest signs of impairment of renal function. There are many who do not agree to this conception, because the uric acid may rise because of extrarenal influences, and its interpretation is difficult on this account. However, if the history and physical findings in any case point to involvement of the kidneys, an elevation of the blood uric acid often indicates an incipient diminution of the functional excretory activity of the kidneys. In many instances the two hour test corroborates this, since nocturnal polyuria and a slight lowering of the urinary specific gravity may accompany the increment in the uric acid of the blood. This question admits of various interpretations, but as we have followed the clinical progress of patients, we have concluded that an elevation of the uric acid in the blood in many instances is indicative of a diminution in the excretory power of the kidneys, even though other tests for renal function may show little or no impairment.

#### THE CREATININE CONTENT OF THE BLOOD

There has been some doubt as to what is really measured by the various methods in use for determining creatinine in the blood. Behre and Benedict<sup>16</sup> are of the opinion that creatinine is present in the blood in extremely small quantities and that what is actually measured is some

<sup>16</sup> Behre, J. A., and Benedict, S. R. Studies in Creatine and Creatinine Metabolism, *J. Biol. Chem.* **52**: 11, 1922.

*The Urea Clearance Test in Relation to Other Tests and Measures of Renal Function in Bright's Disease*

Case Number	Type of Renal Lesion	Blood			Blood Count			Two Hour Test		U/B			Volume of Blood Cleared of Urea			Blood Urea Clearance per Cent of Normal Cs=51 Cm=75
		Urea Nitrogen, Mg per 100 Cc	Uric Acid, Mg per 100 Cc	Creatinine, Mg per 100 Cc	Hemo globin, per Cent	Red Blood Cells, Millions	Specific Gravity (Last Two Figures)	Volume Urine, Cc	With Urine Volume Less Than 1 Cc per Minute	With Urine Volume Between 1 1/2 Cc per Minute	With Urine Volume More Than 2 Cc per Minute	With Urine Volume Less Than 2 Cc per Minute	With Urine Volume More Than 2 Cc per Minute			
1	Acute diffuse glomerular nephritis	14.4					Day Night	05-18 12	700	61.7 53.4			50.0 45.3		92.4 83.9	
2A	Chronic diffuse glomerular nephritis	18.5	5.3	1.2	73	436	Day Night	12-19 11	510	22.6 24.7			12.1 16.0		22.9 29.6	
2B	Chronic diffuse glomerular nephritis	25.1	1.8	3.1			Day Night	09-16 12	560	20.1 20.6			16.3 15.9		30.2 29.5	
2C	Chronic diffuse glomerular nephritis	26.6	1.5		80	106	Day Night	07-15 09	610	19.2 19.9			15.8 16.3		29.3 30.2	
3	Chronic diffuse glomerular nephritis	71.1	10.2		72	375	Day Night	12-16 14	320	~	6.2 5.5		6.7 6.7		12.5 12.1	
4	Chronic diffuse glomerular nephritis	87.1	4.8	8	61	307	Day Night	07-10 19	150	3.8	3.2		3.4 3.3		6.3 6.0	
5	Chronic diffuse glomerular nephritis	69.8			30	175	Day Night	10-12 09	500	5.5 5.5			2.3 2.4		4.2 4.5	
6	Chronic diffuse glomerular nephritis	166.6	7.4	14.3	40	217	Day Night	08-12 12	700	2.5	2.4		2.4 2.4		4.5 4.4	
7	Chronic diffuse glomerular nephritis	147.3	12.2	13.4	69	365	Day Night	08-11 11	48	3.4 2.7			3.0 1.9		5.6 3.5	
8	Chronic diffuse glomerular nephritis	104	6.2	13	46	257	Day Night	10-10 10	250		3.7 3.8		3.9 3.8		7.2 7.1	

9	Chronic diffuse glomerular nephritis	24 4	60	2 9	Day Night		20 6 19 9	13 4 14 2	24 9 26 3
10	Chronic diffuse glomerular nephritis	21 4	81	5 05	Day Night	09-14 06	1000	10 9	29 6
11A	Chronic diffuse glomerular nephritis	11 7	66	3 32	Day Night	06-11 06	600	11 8	
11B	Chronic diffuse glomerular nephritis	31 8	68	3 3	Day Night	02-06 04	860	10 8 9 7	24 2 24 3
12	Chronic diffuse glomerular nephritis	35 3			Day Night	05-12 06	1000	9 6 10 1	23 5 23 2
13	Chronic diffuse glomerular nephritis	17 4	70	1 76	Day Night	17-30 10	1200	59 5 52 2	106 7 94 7
14	Chronic diffuse glomerular nephritis	21 7	82	4 84	Day Night	02-06 01	410	4 3 3 0	10 1 10 8
15	Chronic diffuse glomerular nephritis	14 6	96	6 4	Day Night	04-18 10	590	16 8 12 1	56 1 45 4
16	Chronic diffuse glomerular nephritis	16 2	91	4 74	Day Night	18-28 06	510	34 26 5	69 0 62 3
17A	Arteriosclerotic Bright's disease	16 9	84	5 02	Day Night	11-27 23	510	36 0 43 8	66 6 81 0
17B	Arteriosclerotic Bright's disease	15 5			Day Night	13-18 16	720	30 7 25 3	69 2 71 3
18	Arteriosclerotic Bright's disease	26 9	91	4 78	Day Night	11-16 08	1100	24 9 23 3	16 0 43 1
19	Arteriosclerotic Bright's disease	16 1	72	3 9	Day Night	08-12 10	1100	20 0 19 0	56 6 38 3
20	Arteriosclerotic Bright's disease	26 9			Day Night	11-15 14	320	9 9	18 3 80 8
21	Arteriosclerotic Bright's disease	10 7	80	5 77	Day Night	09-14 18	500	35 9 13 1	66 5 24 2

unknown chromogenic substance. This, of course, does not detract from any clinical application of the so-called creatinine determinations, since in marked renal insufficiency this chromogenic substance is retained in the blood.

It has been appreciated for a long time that creatinine rises in the blood only when renal function becomes markedly impaired (Chace and Myers,<sup>13</sup> Myers, Fine and Lough<sup>14</sup> and Myers and Lough<sup>17</sup>). Our results show that normal creatinine values may be found in the blood with as much as 85 per cent of kidney function lost, as measured by the urea clearance test (table, cases 2a, 12 and 14). When the urea clearance has fallen to about 5 per cent of normal and uremia is impending, the creatinine begins to mount in the blood (table, cases 4, 6, 7 and 8). This is in full accord with the findings of Van Slyke and his associates.<sup>2</sup>

#### THE HEMOGLOBIN PERCENTAGE AND THE RED BLOOD CELL COUNT

The fact that anemia is associated with impairment of renal function has been appreciated since the days of Bright. More recently, Brown and Roth<sup>18</sup> showed that the degree of anemia is directly proportional to the increase of creatinine in the blood, and they stressed the prognostic value of their data. Ashe<sup>19</sup> has shown in a detailed study of 136 cases of Bright's disease, that the severity of the anemia and the degree of renal insufficiency run a parallel course. The anemia at times resembles an extreme secondary type and at others, the pernicious type with a high color index. He observed the latter state more frequently in patients with marked renal insufficiency, and expressed the belief that the damage to the liver usually present in such cases may account for the relatively high hemoglobin percentage.

Van Slyke and his associates<sup>2</sup> have shown that the hemoglobin content of the blood is likely to fall much later in the disease than the blood urea clearance. This seems to be in accord with the view held by Ashe,<sup>20</sup> who believes that renal insufficiency must exist for a variable period

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17 Myers, V. C., and Lough, W. G. The Creatinine of the Blood in Nephritis. Its Diagnostic Value, *Arch Int Med* **16** 536 (Oct.) 1915.

18 Brown, G. E., and Roth, G. M. The Anemia of Chronic Nephritis, *Arch Int Med* **30** 817 (Dec.) 1922. The Prognostic Value of Anemia in Nephritis, *J A M A* **81** 1948 (Dec 8) 1923.

19 Ashe, B. The Hemoglobin Percentage and the Red Blood Cell Count in Bright's Disease, Myocardial Insufficiency and Hypertension, *Arch Int Med* **44** 506 (Oct.) 1929.

20 Ashe, B. Anemia in Bright's Disease in Mosenthal, H. O. Diagnosis and Treatment of Variations in Blood Pressure and Nephritis, *Oxford Monographs on Diagnosis and Treatment*, vol. 7, edited by H. O. Christian. New York, Oxford University Press, 1930.

before the anemia becomes manifest. The uremic patients with less than 10 per cent of renal function as measured by the blood urea clearance who showed hemoglobin contents above 80 per cent of normal, as reported by Van Slyke, McIntosh and their co-workers,<sup>2</sup> were patients with acute diffuse glomerular nephritis in whom the marked degree of renal insufficiency was transient.

In patients with chronic diffuse glomerular nephritis with urea clearances definitely below the normal level in whom renal insufficiency has existed for several weeks or months, secondary anemia is usually present, the intensity of which generally, though not invariably, is in direct proportion to the degree of impairment of renal function and the duration of the insufficiency.

The retention uremia associated with chronic diffuse glomerular nephritis is, in our experience, always accompanied by a marked degree of anemia. Cases 4 to 8 (table) illustrate the severe degrees of anemia (and the high color indexes) that may be encountered in the uremia terminating the chronic nephritides. This is, in reality, a restatement of the fact that the anemia is as a rule directly proportional to the degree of renal insufficiency.

#### THE RATIO OF URINE UREA CONCENTRATION TO BLOOD UREA CONCENTRATION

Van Slyke and his associates<sup>2</sup> compared the standard blood urea clearance and the ratio of urine urea concentration to blood urea concentration ( $U/B$  ratio) in a series of nephritic subjects and concluded that of all the tests they examined, the determination of the  $U/B$  ratio was the only one that approximated in sensitiveness the measurement of the blood urea clearance. Harrison<sup>21</sup> stressed the fact that consistent results may be obtained with the  $U/B$  ratio in nephritic subjects if the volume of urine is less than 2.5 cc per minute. Van Slyke and his collaborators<sup>2</sup> have shown that the  $U/B$  ratio approximates the standard clearance only when the urine volume is less than 2 cc per minute.

We have tabulated our results in three columns (table)—cases with volumes of urine of less than 1 cc per minute, those with volumes between 1 and 2 cc per minute and those with volumes of more than 2 cc per minute. A study of our protocols shows that, with urine volumes of more than 2 cc per minute, the  $U/B$  ratio bears no relationship to clearance values. A close approximation between the  $U/B$  ratio and the standard clearance is obtained with urine volumes between 1 and 2 cc per minute. With urine volumes much less than 1 cc per minute (oliguria) the  $U/B$  ratio deviates appreciably from the standard clearance.

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<sup>21</sup> Harrison, G. A. On Urea Tests of Renal Function, *Brit J Exper Path* 3: 28, 1922.



## THE TWO HOUR TEST FOR RENAL FUNCTION

The two hour test for renal function was formulated by Hedinger and Schlayer in 1914. It was adapted by Mosenthal,<sup>21</sup> in 1915, to diets customary in the United States. Subsequently, in 1918, it was shown that types of diet within extremely wide limits were suitable for the test (Mosenthal<sup>22</sup>). The various concentration and dilution tests, so successively initiated by Volhard, are essentially similar to the two hour test for renal function, since they depend on the interpretation of the volume of urine eliminated and on the power of the kidney to concentrate and dilute the urine, as measured by the specific gravity. For more than ten years, we have carried out the two hour test on patients who were ambulatory and eating their customary diet, with satisfactory results. The table shows the degree of variation in the specific gravity of the urine excreted during the day and the specific gravity and the volume of the urine excreted during the night.

In the interpretation of the results of the two hour test, all possible modifying factors have been excluded, that is, influences other than renal, such as cardiac decompensation, the elimination of edema, pyelitis, cystitis, etc., which distort the true readings of specific gravity and volume, have been eliminated. Normal renal function is demonstrated by a 9 point variation or more of the specific gravity of the urine voided in twenty-four hours. The maximal specific gravity of any one specimen should be 1.020 or higher. The night volume of urine (measured from three hours after the evening meal to the rising hour the following morning) should not exceed 725 cc. Mosenthal<sup>22</sup> stated

With diminished renal function, the night volume is prone to increase so that it may be necessary for the patient to void one to four or more times a night. The nocturnal polyuria apparently is a process of elimination which compensates for a diminished excretion during the day. Nocturnal polyuria often is a very early sign of impairment of renal function in Bright's disease, it is of great significance when present.

The standard urea clearance of Moller, McIntosh and Van Slyke<sup>23</sup> expresses the number of cubic centimeters of blood of which the urea content is concentrated into 1 cc. A normal standard clearance of 54 cc of blood (100 per cent of urea clearance) indicates that the kidneys concentrate the blood urea fifty-four times under these conditions. It follows, therefore, that the standard clearance may be interpreted as the concentrating power of the kidney, and the corollary presents

<sup>22</sup> Mosenthal, H. O. Variations in Blood Pressure and Nephritis, Oxford Monographs on Diagnosis and Treatment, vol. 7, edited by H. O. Christian, New York, Oxford University Press, 1930.

<sup>23</sup> Moller, E., McIntosh, J. F., and Van Slyke, D. D. Studies of Urea Excretion. II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, J. Clin. Investigation 6: 427, 1928.

itself that the standard urea clearance and the specific gravity of the urine (which is really an index of the concentration of urinary solids by the kidney) should parallel one another. Our results, however, do not show this to be true in all cases.

Cases 2*a*, 2*b* and 2*c* (table) show that there may be fairly good concentration of the day urine with only 30 per cent of renal function as measured by the urea clearance test. In such instances, however, the specific gravity of the night urine shows that some renal insufficiency exists. Although specific gravity readings do not actually parallel the urea clearance values, all cases with urea clearances of less than 50 per cent of the average normal value suggest impairment of renal function as measured by the two hour test.

With clearance values below 10 per cent of normal (table, cases 4 to 8) there is always fixation of the specific gravity of the urine at a low level (from 1.010 to 1.012), indicative of maximal renal insufficiency. With clearance figures between 10 per cent and 30 per cent of normal, the variation of the specific gravity of the day urine is diminished, the maximal specific gravity of 1.020 is never reached, the specific gravity of the night urine is always low, and there may be nocturnal polyuria (table, cases 2, 3, 11*b*, 12 and 14). With urea clearance values between 30 per cent and 50 per cent of normal, the two hour test usually shows definite impairment of renal function in one or more of the characteristics mentioned (table, cases 10, 11*a* and 18).

In occasional instances, the urea clearance test showed graver impairment of renal function than was suggested by the result of the two hour test. In other cases, normal urea clearance values were obtained in the presence of a definitely decreased specific gravity of the night urine and marked nocturnal polyuria. In the latter case (table, case 13), the interpretation of the two hour test was slight renal insufficiency, whereas the clearance test gave normal figures.

#### COMMENT

A careful study of all the data obtained by the various measures and tests for renal function in the study of Bright's disease yields several pertinent facts. It is our belief that no single test for the determination of renal efficiency is to be preferred above all others in the evaluation of renal function, and this is especially true when little or no impairment exists.

The urea clearance test is a valuable index of renal function and in the great majority of cases shows a decreased ability of the kidney to excrete urea before there is any evidence of nitrogen retention in the blood. It should be emphasized, however, that occasionally a patient

may show a definite increase of uric acid in the blood which could be explained only on the basis of slight renal insufficiency, while the urea clearance test shows normal renal function. We have observed cases with marked nocturnal polyuria explainable only on the same basis with normal blood urea clearance values. Wakefield, Power and Keith<sup>24</sup> demonstrated identical findings for the inorganic sulphates in the serum in early renal insufficiency. In the critical analysis of cases of Bright's disease with only slight impairment of renal function, it is necessary, indeed imperative to carry out as many of the tests and measures of renal function as possible in order to determine the status of renal efficiency from all angles. No single test evaluates renal function in all its physiologic and pathologic aspects.

The degree of anemia in Bright's disease parallels the amount of renal insufficiency, provided the impairment has existed for some time. It follows, therefore, that the urea clearance test will show impairment of renal function for some time before the anemia becomes apparent. In the chronic nephritides, in which a definite degree of renal insufficiency has existed for several weeks and longer, the degree of anemia is indicative of the amount of functional impairment as determined by the urea clearance test.

When satisfactory clearance studies cannot be made because of bladder retention, incontinence, etc., Van Slyke and his associates<sup>2</sup> suggested calculating the  $U/B$  ratio, when the urinary rate is known to be less than 2 cc per minute. Under such conditions, they state, the  $U/B$  ratio approximately equals the standard clearance. Our results agree with those of Van Slyke and his collaborators, but it should be pointed out that in oliguric patients the  $U/B$  ratio may deviate appreciably from the standard clearance and the calculation of the percentage of normal renal function may give somewhat higher readings. In general, it may be stated that the  $U/B$  ratio may be used in place of the standard clearance when for some reason accurate urine volumes cannot be obtained and the volume is known to be less than 2 cc per minute. In patients with bladder retention or incontinence it appears to us more advisable to obtain definitely timed specimens of urine by catheterization and thus determine either the standard or the maximum urea clearance. We have always felt hesitant about accepting the  $U/B$  ratio as an index of renal function when it was impossible to gage even approximately the urine output.

Inasmuch as the blood urea clearance under standard conditions of urinary excretion determines the ability of the kidney to concentrate urea, it was felt that the determination of the specific gravity of the

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<sup>24</sup> Wakefield, E. G., Power, M. H., and Keith, N. M. Inorganic Sulphates in the Serum in Early Renal Insufficiency, *J. A. M. A.* 97:913 (Sept. 26) 1931.

urine, as outlined in the two hour test, would parallel rather closely the blood urea clearance. This expectation has not been fulfilled in every detail. In some cases, the urea clearance test shows a greater degree of renal impairment than could be surmised from the results of the two hour test. In other instances, determination of the specific gravity of the urine and the measurement of the night volume of urine suggested impairment of renal function while the urea clearance test gave normal values. In marked or maximal renal insufficiency, the two hour and urea clearance tests indicate the same degree of impairment.

The two forms of tests do not measure the efficiency of the same functions of the kidney. The urea clearance test gages the ability of the kidneys to eliminate urea. This may be successfully accomplished although only a small amount of urine is secreted within a given unit of time, that is, there is an impairment of the renal parenchyma as far as water excretion is concerned, as in the oliguric stage of acute diffuse glomerular nephritis. On the other hand, the elimination of urea may be normal although the power of concentration has been distinctly diminished, as is seen in the compensatory polyuria of certain stages of chronic nephritis. The tests of specific gravity furnish information as to the ability of the kidney to concentrate and to dilute, they indicate by what emergency and compensatory means the elimination of urea and of other solids is maintained. In the earlier stages of impairment of renal function occurring in chronic Bright's disease, each of these tests, the specific gravity and the urea clearance test, tells a story of its own. In the later stages, when all the functions of the kidney are more or less equally involved, both procedures will indicate a similar degree of diminution of renal function.

There are certain conditions that affect the specific gravity of the urine, and these must always be kept in mind when one is interpreting the results of the two hour test which apparently do not influence the blood urea clearance. In Bright's disease with edema, the specific gravity of the urine will be increased or decreased by the deposition or the elimination of edema, respectively. In acute diffuse glomerular nephritis, the specific gravity of the urine often reaches surprisingly high and fixed figures. Irritation of the urinary tract, as caused by cystitis and pyelitis, tends to decrease the specific gravity of the urine. The urea clearance test is not markedly influenced by such factors.

The clearance test requires exactitude in collecting all the urine voided in a specified time, and this is often impossible in certain conditions of the bladder, notably retention of urine due to prostatic hypertrophy or incontinence from any cause. In such cases, the two hour test is of distinct advantage, since the urine need not be timed accurately. Again, the simplicity of the latter test is especially suited for the active hospital service or the physician's office.

In retrospect, it seems only fair at this time to emphasize again the necessity of investigating renal function from all possible angles, especially in early renal insufficiency. One or more of the tests or measures at the disposal of physicians may indicate slight impairment of renal function while others reveal normal renal function. It is obvious that the complexity of early functional pathologic conditions of the kidney is not determined by any single test. The urea clearance test is of considerable clinical value and should add materially to a better understanding of the function of the kidney as more work along such lines is accomplished.

#### SUMMARY

The urea clearance test usually demonstrates impairment of renal function before the urea, uric acid or creatinine is increased in the blood. Occasionally, cases of early renal insufficiency may show an elevation of the blood uric acid before the urea clearance test implies any impairment. In the chronic nephritides with definitely impaired renal function of some weeks' or months' duration, the degree of anemia parallels the amount of insufficiency as measured by the urea clearance test. The *U/B* ratio approximates the urea clearance values with urine rates less than 2 cc per minute, it deviates appreciably from the standard clearance in oliguric patients, it bears no relation to the standard clearance with urinary rates of more than 2 cc per minute. In cases of Bright's disease with less than 50 per cent of renal function as measured by the urea clearance test, the two hour test usually demonstrates impairment of renal function, occasionally, the two hour test may suggest slight renal insufficiency while the urea clearance test gives normal values, in other instances, the urea clearance test suggests graver degrees of impairment of renal function than can be surmised from determinations of the specific gravity and volume of the urine.

# SEDIMENTATION TEST AS A ROUTINE LABORATORY PROCEDURE

OBSERVATIONS ON ELEVEN HUNDRED PERSONS

HERBERT J. SCHATTENBERG, M.D.

NEW ORLEANS

In 1918 Fahraeus,<sup>1</sup> in Germany, demonstrated the clinical importance of variable accelerated sedimentation of the erythrocytes in different conditions of disease. Westergreen,<sup>2</sup> also in Germany, carried out excellent work in this line, however, his technic is more elaborate and difficult, and his observations were chiefly on the sedimentation of red blood cells in tuberculosis. In America, Polak<sup>3</sup> is the most outspoken advocate of the sedimentation test. From its application in gynecologic conditions, he believes that this test offers another aid in the diagnosis of an infection which when frequently repeated and correlated with the clinical history, temperature curve and white blood cell changes forms a valuable index as to the time at which to operate and is also of prognostic value.

To explain the differences in speed of erythrocytic sedimentation, Fischl<sup>4</sup> and Schmitz<sup>5</sup> held that it is due to an alteration of the albumin-globulin ratio with an increase of the globulin. Kurten<sup>6</sup> expressed the belief that the increased sedimentation is due to an increased blood cholesterol. Fahraeus<sup>1</sup> stated that increased sedimentation is produced by an alteration in the electrical charge of the blood corpuscles, causing a loss of their repelling force and thereby bringing about their agglutination and more rapid sedimentation. Reyner<sup>7</sup> held that a difference in surface tension of the blood plasma is responsible for the phenomenon. He attempted to prove this by adding formaldehyde to the blood speci-

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These observations were made possible through the courtesy of the Dallas City Health Department and the Out-Patient Dispensary of Baylor Hospital

- 1 Fahraeus, J. *Biochem Ztschr* **89** 335, 1918
- 2 Westergreen, A. *Brit J Tuberc* **15** 72, 1921
- 3 Polak, J. O. *Clinical Significance of the Sedimentation Test*, J. A. M. A **90** 72 (Jan 14) 1928
- 4 Fischl, K. *Am Rev Tuberc* **10** 606, 1924
- 5 Schmitz, H. *Am J Obst & Gynec* **11** 353, 1926
- 6 Kurten, H. *Arch f d ges Physiol* **185** 248, 1920
- 7 Reyner, C. E. *The Sedimentation of Red Blood Cells*, J. Lab. & Clin. Med. **14** 630 (April) 1929

men to increase the surface tension and claimed that a decrease in red cell sedimentation happened in direct proportion to the amount of formaldehyde added. Hunt<sup>8</sup> felt that whatever is responsible for increased sedimentation is contained in the blood plasma, and that it is most likely an increase in the fibrinogen. Gradwohl<sup>9</sup> claimed that the hydrogen ion concentration influences sedimentation, since acidosis reduces and alkalosis accelerates the rate. This is due to the effect of these factors on flocculation and agglutination of the albuminous substances in the plasma.

#### TECHNIC

The value of any test depends on its simplicity of technic, its applicability and the additional information that it affords as compared with other diagnostic methods or when correlated with them. A great number of different methods are used in making this determination. The two best known German methods are those of Westergreen<sup>2</sup> and Linzenmeier. The standard American method is that of Cutler,<sup>10</sup> which is a modified and simplified Westergreen technic. It calls for a small tube 5 mm in diameter and marked in millimeters beginning with 0 at the 1 cc level and ending with 50 mm at the bottom. One-tenth cubic centimeter of 3 per cent sodium citrate is first drawn into a hypodermic syringe to act as an anticoagulant, then 1 cc of the patient's blood is drawn into the syringe. In order to facilitate the mixing of citrate and blood, a small bubble of air is drawn into the syringe. The syringe content is then emptied into a Cutler tube. A reading of the number of millimeters' drop in the red blood cell column is taken every ten minutes and recorded as shown in the chart.

It has been shown by the Cutler technic that in acute infectious processes the greatest fall in the red cells will take place in the first hour and that readings may be discontinued following the six readings at ten minute intervals. In this respect the Cutler procedure has a great advantage over that of Linzenmeier, in which a mark is made on the tube at the 18 mm level and a record made of the time when the blood cell column falls to this level which may be in from thirty minutes to twenty-four hours. Naturally, the observer's time and attention are therefore focused on this procedure for a period varying from thirty minutes to twenty-four hours.

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<sup>8</sup> Hunt, H. F. *J. Lab. & Clin. Med.* **14** 1061, 1929.

<sup>9</sup> Schilling, V. *The Blood Picture and Its Clinical Use*, translated by R. B. H. Gradwohl from 7th and 8th German editions, St. Louis, C. V. Mosby Company, 1929.

<sup>10</sup> Cutler, in Nicholson, Daniel. *Laboratory Medicine*, Philadelphia, Lea & Febiger, 1930, p. 77.

## THE VALUE OF THE SEDIMENTATION TEST IN VARIOUS CONDITIONS

It is my opinion that the sedimentation test will prove of great value if those physicians interested in medical diagnosis, preventive medicine, public health or life extension departments of insurance companies make the sedimentation test as a routine for all persons presenting themselves for physical examination. It is true with only a few exceptions, such as those of pregnancy and menstruation, that there can be an accelerated sedimentation rate only when there is a disease process or a destruction of tissue going on in the body. The test is not indicative of any one particular disease, but when the rate is markedly accelerated in a person who applies for a physical examination, it assures the examiner that there is trouble in this patient's body, and that he must reexamine him more carefully and more thoroughly to ascertain its exact nature.

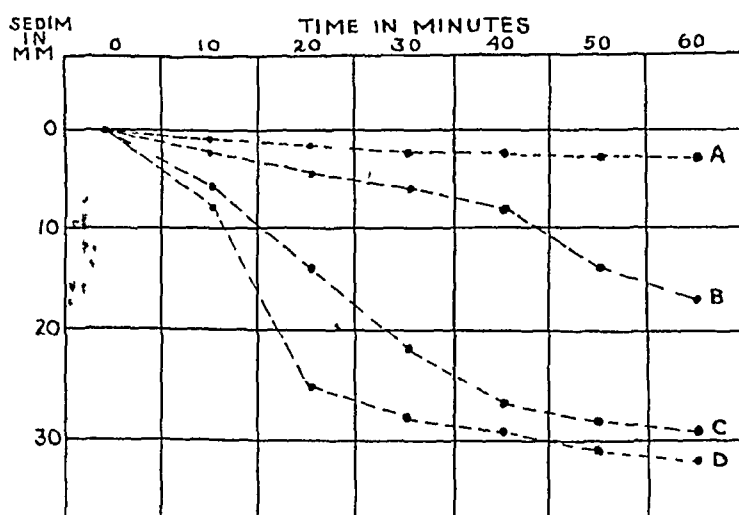


Chart after Nicholson (Laboratory Medicine, Philadelphia, Lea & Febiger, 1930, p 80) *A* represents a normal curve, *B*, a clinically quiescent process, *C*, a clinically slightly active process, and *D*, a clinically markedly active process

With the foregoing considerations in mind, and knowing how much this test would help the examiner in obscure and latent stages of various diseases, my associates and I decided to make the test as a routine for applicants presenting themselves for examination for the purpose of obtaining health cards in the Dallas City Health Department. Tests were made also on patients in the outpatient dispensary of Baylor Hospital. The results obtained have been interesting. In every person presenting an accelerated sedimentation we have been able to find the cause in the form of some disease process. In all, eleven hundred persons were tested for their sedimentation rates. Since all applicants received also a routine Wassermann blood test, there was an excellent opportunity to see what the sedimentation test showed in the persons whose blood gave a positive Wassermann reaction. Approximately 40 per cent of these showed accelerated red cell sedimentation, and in all



of the latter there was shown some form of open lesion or a very active syphilitic process. Those whose blood gave a positive Wassermann reaction without an accelerated red cell sedimentation appeared to have latent syphilis, or showed no active clinical or outward appearance of syphilis.

Besides the persons described with positive Wassermann reactions and markedly accelerated sedimentation rates in whom open or active syphilitic lesions were found, six additional ones were found with rapid sedimentation rates. On further and more thorough clinical examination of these six, one was found to have myeloid leukemia, one pellagra, one incipient pulmonary tuberculosis, two subacute salpingitis and one pityriasis rosea. The conditions named were discovered only after accelerated sedimentation rates had focused further attention on these patients. From this it may be seen what an aid one has in this test when it is made as a routine for all persons presenting themselves for physical examination.

In gynecology, the sedimentation test may indicate the best time at which to perform a nonurgent operation. A patient showing a sedimentation rate of over 18 mm in an hour, if operated on for pelvic disease, is apt to have a stormy convalescence. A reading of 18 mm in thirty minutes is easily found in cases of acute pelvic abscess, and if the patient is operated on, conservative evacuation should be employed. In the differentiation between ectopic pregnancy and acute exacerbation of a chronic inflammatory process, a rapid sedimentation points toward infection, while a slow sedimentation indicates ectopic pregnancy. With cysts or uterine fibroids, the sedimentation is normal, provided there is no complicating infection or degenerative change in the cyst or fibroid. The sedimentation test is valueless after the third month of pregnancy and for the first two weeks of the puerperium, as then readings cannot be attributed to infection. Furthermore, after the fourth month of pregnancy there are so many clinical and physical signs to assist in the diagnosis of pregnancy that there is no need to use sedimentation. In pelvic infection, the sedimentation test is far more reliable than leukocytic counts. It is well known that leukocytic counts may fluctuate from high to low levels during a twenty-four hour period, consequently, there is danger of the surgeon's taking a blood specimen when the fluctuation is at a low level and considering that the time for operation is at hand, whereas, if the count is repeated in several hours, it will be found again dangerously high. This error never happens with the sedimentation test. When the sedimentation rate indicates an active process the rate can be shown to return to normal slowly and gradually as the patient's condition improves. Irregular fluctuations do not occur with this procedure as with leukocytic counts. In fact, Polak believes that the sedimentation test never yields erratic results. Furthermore, he is of the opinion that this test is the best indicator as to the time most suitable for

the patient's discharge from the hospital. Polak stated, "Previously, we have felt safe in discharging a patient when she had a normal temperature for one week and a normal leukocyte count, even in the presence of pelvic exudate. Many of these types of patients on returning home and assuming their usual household and social duties have been seized with severe pelvic pain and rise in temperature. These women have returned with increased exudate and tenderness and in need of immediate hospitalization. All this could have been avoided had the patient been kept in the hospital until the sedimentation time had returned to normal."

In tuberculosis, Cutler<sup>10</sup> considers the sedimentation rate of more value in estimating the activity of a tuberculous process than the pulse rate, temperature or weight. The pulse rate and the temperature may return to normal while the process is still more or less active. The sedimentation rate does not return to normal until the tuberculous lesion is well encapsulated, therefore, this test should be run as a routine in hospitals for tuberculosis on all patients at intervals of a month or oftener to keep a check on their progress.

#### SUMMARY

1. A standard technic for the performance of the sedimentation test should be accepted. There are too many modifications of the sedimentation test extant. That of Cutler is the most applicable, since it gives one the benefit of the first hour's readings, which are the most important, at ten minute intervals. Furthermore, the observer's time is taken up for a period of one hour only.

2. A normal sedimentation rate with but few exceptions rules out the presence of disease. Since there is a physiologic increase in fibrinogen during menstruation and pregnancy, one naturally expects a rapid sedimentation of red blood cells to occur.

3. The sedimentation test is useful in the differential diagnosis of gynecologic conditions.

4. It is useful in determining the proper time for nonurgent elective operations, in prognosticating postoperative complications after the first week and as a criterion for discharging patients.

5. In active tuberculosis, the sedimentation rate is always rapid, regardless of physical findings, it is also of more value than are the pulse rate, temperature and weight in checking treatment in a tuberculous patient.

6. In health departments, it assists in the diagnosis of obscure diseases that would otherwise escape detection. Accelerated sedimentation means destruction of tissue, and the examiner therefore reexamines the patient to ascertain the nature of the pathologic process that was overlooked the first time.

# METHEMOGLOBINEMIA

WILLIAM J. DIECKMANN, M.D.

CHICAGO

Methemoglobinemia occurring spontaneously is rare, and a case of twenty-seven years' duration is, so far as I know, unheard of. The first cases were described in 1902, by Stokvis<sup>1</sup> and Talma,<sup>2</sup> who considered the cyanosis to be due to methemoglobin, but van den Bergh,<sup>3</sup> in 1905 in a study of two cases, was able to distinguish two types of this condition, which had been known and is still known as "enterogenous cyanosis." He showed that the cyanosis was due in one of his cases to sulphhemoglobin and in the other to methemoglobin circulating in the blood. Up to that time there had been no differentiation between the two types, and some doubt, therefore, arises as to the true nature of the cases described by Stokvis and Talma. Excluding then four cases because of this doubt, I have been able to collect the following reports of six cases of methemoglobinemia of unknown origin.

## REPORT OF CASES

VAN DEN BERGH<sup>3</sup> (1905) —A man, aged 25, complained for seven years of weakness, cyanosis, edema and intermittent diarrhea and constipation. A milk diet gave only temporary improvement.

VAN DEN BERGH AND GRUTTERINK<sup>4</sup> (1906) —Case 1. A man, aged 34, stated that for four years he had had dysentery, headache, a feeling of paralysis of the legs and arms and cyanosis.

Case 2. A man, aged 51, gave a similar history.

GIBSON AND DOUGLAS<sup>5</sup> (1906) —A woman, aged 36, complained of weakness, headache, cyanosis and diarrhea of three years' duration, together with a change in complexion and color of the hair. There had been free use of aniline derivatives, but the cyanosis persisted when the drugs were stopped. Nitrites were present in both the saliva and the blood. *Bacillus coli* was recovered in pure culture from the blood, and presumably was a factor in the production of the "microbic cyanosis," as it was called by the authors.

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1 Stokvis, B. J. von Levden's *Restschrift, Internat. Beitr. z. inn. Med.* **1** 597, 1902.

2 Talma, S. *Berl. klin. Wchnschr.* **39** 865, 1902.

3 van den Bergh, A. A. H. *Deutsches Arch. f. klin. Med.* **83** 86, 1905.

4 van den Bergh, A. A. H., and Grutterink, A. *Berl. klin. Wchnschr.* **43** 7, 1906.

5 Gibson, T. A., and Douglas, C. C. *Lancet* **2** 72, 1906.

LLOYD<sup>6</sup> (1924)—A nurse, aged 26, was admitted to the hospital because of attacks of abdominal pain, associated with cyanosis. She dated the onset of her condition to a strain caused by lifting a patient. She was seen at the hospital at irregular intervals for four years, and although several laparotomies were performed, including resection of the colon, there was no permanent relief. The blood, which at first contained methemoglobin, soon contained sulphemoglobin instead. A report of the same case in 1928 by Waterfield<sup>7</sup> showed that at this time the blood contained both methemoglobin and sulphemoglobin. The patient eventually died. The total duration of the cyanosis was seven years, of which time more than two years were spent in the hospital.

MILLER<sup>8</sup> (1930)—Enterogenous methemoglobinemia occurred in a 9 year old girl. The foster mother, who had obtained the child at 9 months of age, stated that she was blue at that time and had been blue from birth. The color of the hair varied with the degree of cyanosis. Methemoglobin was demonstrated by spectroscopic examination, and although the child was followed for two years there was no improvement. Some relief resulted from colonic irrigations with a 1:4,000 solution of potassium permanganate. It was also noted that an increase of indican in the urine was always followed within from twenty-four to forty-eight hours by cyanosis.

AUTHOR'S CASE—N. B., a white woman, aged 27, was admitted to the hospital on Feb 16, 1931, because of cyanosis. She stated that her skin had been blue from birth, with an increase in intensity during pregnancy. Her husband stated that the color had been the same since he first met her. Several years before admission, she took "bromoseltzer," and for the past three months, she had taken 10 grains (0.65 Gm) of acetylsalicylic acid daily because of "neuralgia in her teeth." At the time of admission she was pregnant for the third time, and she was at term on March 16, 1931. Both previous pregnancies had been terminated by delivery with forceps because of "weak pains." The first baby was stillborn, and the second died at the age of 3 months.

The note of the cardiologist was as follows: "The patient has been blue all her life, but has never had any symptoms of cardiac impairment. There is cyanosis of the fingers, nose and face, especially around the nose. There is no clubbing of the fingers. The heart shows no enlargement on percussion. There is a systolic murmur in the third left interspace. The pulse rate is 120. There is no evidence of organic or acquired heart disease, but with the tachycardia and cyanosis of long standing, congenital heart disease is quite likely." The electrocardiogram showed tachycardia.

Blood was obtained for a determination of oxygen saturation, and was also used for a routine chemical analysis. As a routine hemoglobin was determined as carboxyhemoglobin (colorimetrically), and in this case the technician noted that the unknown carboxyhemoglobin solution could not be made to match the standard satisfactorily. When the hemoglobin was determined by the oxygen capacity method, only 8.8 Gm was found, in contrast with 11 Gm when it was determined as carboxyhemoglobin. The discrepancy was even greater when it was determined as acid hematin. The marked variations in hemoglobin, as determined by different methods, indicated an abnormal form of hemoglobin, and spectroscopic examination showed a large amount of methemoglobin. This compound does not combine with oxygen or carbon monoxide, and the higher reading with the colorimetric determination as carboxyhemoglobin was due to the presence of

6 Lloyd N. L. Guy's Hosp Rep 74 376 1924

7 Waterfield, R. L. Guy's Hosp Rep 78 265, 1928

8 Miller, R. Arch Dis Childhood 5 73, 1930

methemoglobin The determination of acid hematin gave both hemoglobin and methemoglobin, but again the results would not have been questioned had it not been for the determination of oxygen capacity

On February 27, the cardiologist stated that "because of the practically negative heart findings and the presence of methemoglobinemia, a diagnosis of the latter is more likely than one of congenital heart disease"

On March 3, the patient went into labor, and because there was only 7 Gm of functioning hemoglobin per hundred cubic centimeters of blood, she was given 600 cc of citrated blood The blue color almost disappeared following the transfusion and was much less noticeable up to her discharge on March 17, 1931 She was delivered of a 3,700 Gm normal baby after an easy seven hour labor The erythrocyte count varied from 4,330,000 to 5,110,000 The pulse rate ranged from 80 to 100 ante partum and from 70 to 90 post partum

During the period in the hospital everything was done to prevent the ingestion of drugs Cultures made from the mouth and stools were negative for the nitrosobacillus Purgation had no effect on the cyanosis

The patient was seen on April 14, she was again cyanotic Examination of the blood showed that methemoglobin was present in large amounts The essential data have been tabulated (table)

*Results of Determination of Hemoglobin*

Date	Hemoglobin (Gm) Determined as				Hematocrit, per Cent	Methemoglobin, Spectroscopic
	Oxygen Content	Oxygen Capacity	Carboxy hemoglobin	Acid Hematin		
2/19/31	7.2	8.8	11.0	12.7	34	Large amount
2/24/31	7.7	8.6	10.4	11.9	34	Large amount
2/25/31			V-10.0		36	Large amount
3/3/31	Delivered—blood transfusion 600 cc					
3/12/31		V*-11.9	12.9		42	Faint trace
4/14/31	8.9	10.6	11.3	14.2	38	Large amount

\* V = Venous

Clinically, methemoglobinemia is reported most frequently in factory workers, whose skins or lungs come into contact with aromatic coal tar derivatives such as aniline, nitrobenzene and the nitrophenols Reports of cases of methemoglobinemia due to the excessive use of acetanilid are also rather common, but the occurrence of the condition spontaneously is rare, and the etiology is unknown Van den Bergh and Grut-terink stated that they had found nitrites in the blood and assumed that they were the cause of the condition However the origin of the nitrites has not been determined, although in 1913 Mackenzie-Wallis<sup>9</sup> found in the saliva of four patients suffering from sulphhemoglobinemia a nitrite-producing bacillus He also found that the serum of each patient contained a substance capable of reducing oxyhemoglobin to hemoglobin, and he therefore suggested that the sulphhemoglobinemia depended on the absorption of nitrites from the saliva and of small quantities of hydrogen sulphide from the colon His results have not been confirmed

<sup>9</sup> Mackenzie-Wallis R. L. Quart J Med 7:73, 1913

The outstanding feature of methemoglobinemia is cyanosis and, if the condition is severe, dyspnea. The cyanosis is due to the dark brown color of methemoglobin and appears to be more intense than cyanosis produced by a similar concentration of reduced hemoglobin in the blood. The dyspnea is referable to the anoxemia caused by diminution in the oxygen-carrying capacity of the blood.

The discovery of methemoglobin in the case reported was accidental, but the possibility of its occurrence in all cases of cyanosis should be kept in mind. The diagnosis of methemoglobinemia was based on the following spectioscopic examination. The citrated blood was diluted with nine volumes of water and examined spectroscopically. A band centering at 638  $\mu$  was found. Solutions of methemoglobin gave a similar absorption band. The band disappeared on the addition of sodium hydrosulphite. This excludes the possibility that the pigment was sulphemoglobin.

The usual purpose of a determination of hemoglobin is to ascertain the concentration of a functional blood pigment, that is, pigment which carries oxygen. Since no known hemoglobin derivative exhibits this property, the presence of such substances as methemoglobin, carbon monoxide hemoglobin and sulphemoglobin in blood, when knowledge of the concentration of hemoglobin alone is desired, leads to erroneously high results with all colorimetric methods.

In the Newcomer method, methemoglobin, like hemoglobin, is converted into acid hematin by hydrochloric acid. The same interference occurs in other methods involving the formation of acid hematin (e.g., the Sahli method).

In the Palmer method, methemoglobin interferes with the determination merely because of its tinctorial powers, it does not react with carbon monoxide.

The presence of methemoglobin in blood may vitiate determinations of oxygen content and capacity (with the Van Slyke procedure) unless certain precautions are observed (the "inactive" pigment does not interfere with the determination per se). Warburg<sup>10</sup> and his co-workers recently reported that mammalian red blood cells treated with amyl nitrite (to convert part of the hemoglobin to methemoglobin) when subsequently incubated with dextrose or lactic acid undergo the following changes. Methemoglobin oxidizes the sugar or lactate and is thereby converted back to hemoglobin. This then picks up oxygen to form oxyhemoglobin. In rabbit's blood regeneration of hemoglobin is rapid, in dogs and in human blood it is less so. Wendel<sup>11</sup> has confirmed and extended these findings.

<sup>10</sup> Warburg, O., Kubowitz, F., and Christian, W. *Biochem Ztschr* **227** 245, 1930.

<sup>11</sup> Wendel, W. B. *Proc Soc Exper Biol & Med* **28**:401, 1931.

The bearing of these phenomena on determinations of oxygen capacity and content is obvious. If blood containing methemoglobin is allowed to stand before the oxygen capacity is determined, the value of this may be significantly increased over that which would have been obtained had the determination been carried out immediately after the sample was drawn. Chilling slows the reaction, but does not inhibit it completely.

On March 12, the glycolytic activity of the blood cells was found to be normal. From this it would seem probable that the patient's blood would rapidly reduce methemoglobin to hemoglobin. The constancy of the methemoglobinemia, then, is probably due to the continued presence or production of a substance capable of oxidizing hemoglobin.

Further experiments were contemplated in the hope that a cause for the formation of the methemoglobin could be found, but the patient could not be persuaded to return to the clinic.

#### SUMMARY

A case of cyanosis due to methemoglobin of unknown origin, which had been present for twenty-seven years, is reported. The accidental discovery in a routine examination warrants the statement that the condition would be detected more frequently if the blood of cyanotic patients were examined spectroscopically. More attention should be given to determination of the oxygen capacity of the blood than to the colorimetric determination of hemoglobin. In the normal person, the results are identical, but in certain pathologic conditions the apparent hemoglobin may be within normal limits and yet the patient be suffering from anemia because a portion of the hemoglobin cannot carry oxygen.

The spectroscopic examinations and the determination of the glycolytic activity were performed by Mr. William B. Wendel in the Laboratory of Biological Chemistry, Washington University.

# A METHOD FOR THE SIMULTANEOUS ENUMERATION OF BLOOD PLATELETS AND RETICULOCYTES

WITH CONSIDERATION OF THE NORMAL BLOOD PLATELET COUNT IN MEN AND IN WOMEN

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The methods so far introduced for the enumeration of the blood platelets are well-nigh legion. Their very number speaks for a lack of standardization in technic. The method presented here has the following advantages: 1. The individual blood platelets, which are kept from clumping, can be seen, studied and counted without difficulty. 2. The reticulocytes can be counted in the same preparation.

The enumeration of the blood platelets becomes important in the study of the hemorrhagic diseases, particularly in purpura hemorrhagica; it is also of great interest and probably of more value than is realized, in the study of the anemias, leukemias and associated disorders. Since the blood platelets are derived from the megakaryocytes of the bone marrow, they should give, in association with a study of the number of reticulocytes and neutrophils, a complete index as to the activity of the marrow.

The chief difficulty encountered in the enumeration of the blood platelets depends on the marked tendency of these bodies to clump together. This difficulty has often led to neglect of this valuable laboratory procedure. Despite this, counting methods have been numerous, although as yet no completely satisfactory procedure has been devised.

There are in general two main methods for the estimation of the blood platelets. The first is the direct or counting-chamber method, in which the blood platelets are enumerated in much the same way as are the red blood cells. The methods of Wright and Kinnicutt<sup>1</sup> and of Buckman and Hallisey<sup>2</sup> are examples of this technic. The second general method is the indirect one, in which the proportion of platelets to red blood cells is determined in a blood smear preparation. The

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1 Wright, J. H., and Kinnicutt, R. A New Method for Counting Blood Platelets for Clinical Purposes, *J. A. M. A.* **56** 1457 (May 20) 1911.

2 Buckman, T., and Hallisey, J. E. Studies in Properties of Blood Platelets, *J. A. M. A.* **76** 427 (Feb 12) 1921.



absolute number of platelets per cubic millimeter is then calculated after the determination of the red blood cell count. The methods of Fonio<sup>3</sup> and Hittmair<sup>4</sup> are examples of this technic. The estimation of the number of blood platelets (whether normal, increased or diminished) by inspection of fixed blood smear preparations may be included among the indirect methods, although obviously it is not to be relied on for more than a rough approximation.

The various disadvantages of the direct or hemacytometer method have been cited by Olef<sup>5</sup> in a recent article. Among them may be mentioned the following: clumping of the platelets during the drawing of blood into the pipet, the impossibility of visualizing the smallest platelets with the high dry objective, the "loss" of some of the platelets in the 100 microns (0.1 mm) space that exists between the level of the counting chamber and the cover glass above it, the sticking of platelets to the sides of the pipet or to the parts of the hemacytometer, and, finally, (when a stain is used) the precipitation of the stain and the resultant confusion of granules of the stain with blood platelets. Attempts have been made to surmount some of these difficulties by various means, without much success. The direct method, although apparently simple in its application, has many inherent sources of error.

The indirect method has been practiced in several different ways. The simplest and least accurate is the estimation of the blood platelets from the ordinary stained blood smear. This suffices for the routine study of blood smears, but it is worthless when an exact figure for the number of the blood platelets is of importance. Numerous methods are used in the counting of the blood platelets indirectly. Those of Fonio,<sup>3</sup> Hittmair<sup>4</sup> and Olef<sup>5</sup> may be cited as examples. Each of them appears, however, to have certain shortcomings, which we have attempted to overcome.

In the method of Fonio,<sup>3</sup> a drop of 14 per cent magnesium sulphate is placed on the finger, which is then punctured through the drop with a lancet. Cover slip preparations are made in the ordinary way by drawing two cover slips apart, and they are stained with Wright's stain. The blood platelets, which swell when they come in contact with the magnesium sulphate solution, are easy to enumerate. However, the act of drawing apart the cover slips in making the blood smear often causes a marked unevenness in the distribution of the platelets,

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3 Fonio, A. Ueber ein neues Verfahren der Blutplättchenzählung, *Deutsche Ztschr. f. Chir.* **117** 176 (June) 1912.

4 Hittmair, A. Die Blutplättchen, *Folia haemat.* **35** 156, 1928.

5 Olef, I. Blood Platelets. An Improved Indirect Method for Their Enumeration, *Arch. Int. Med.* **46** 585 (Oct) 1930.

thereby making the method almost as inaccurate as an estimation from fixed smears stained with Wright's stain

In the method of Hittmair,<sup>4</sup> a drop of blood is placed on a cover slip that has already been prepared with a dried film of brilliant cresyl blue. The cover slip is then dropped on a slide and examined under oil immersion lens. There is no provision, however, for preventing the platelets from clumping. In addition, their distribution is usually very uneven.

In the method of Olef,<sup>5</sup> extravagant precautions are taken to prevent the platelets from clumping. The drop of blood is allowed to fall into a small paraffin cup which contains a solution of sodium metaphosphate. A paraffin-coated wooden applicator is used to stir the resultant mixture, and a drop of this diluted blood is transferred to a slide over which is placed a cover slip. The blood platelets are then counted, the oil immersion lens being used. No stain is used. This method is accurate, but it has two distinct disadvantages. 1 It involves the use of a special apparatus, however simple. 2 There is no provision for staining the blood platelets, some of which may be missed.

#### METHOD

This is an indirect method in which the diluting fluid is not only isotonic but contains brilliant cresyl blue for staining purposes and sodium citrate for use as an anticoagulant. This solution, which is a modification of the one devised by Buckman and Hallisey<sup>2</sup> for counting the platelets directly, contains the following ingredients:

	Gm or Cc
Brilliant cresyl blue	0.15
Sodium citrate	0.40
Sucrose	8.00
Water	100.00

The cane sugar and the sodium citrate are dissolved in distilled water to which is then added the brilliant cresyl blue. The resulting solution is mixed well and filtered. Three drops of a solution of formaldehyde (1:10) U. S. P., are added as a preservative.

This solution keeps well in a cold place, but it should be filtered every three or four weeks. It has the following advantages: 1 The stained platelets are easily seen. 2 The stained network and granules of the reticulocytes are well brought out. 3 The anticoagulant prevents clumping of the platelets. 4 The isotonicity of the solution aids in the proper separation and distribution of the blood cells.

One of the fingers is well cleaned with alcohol or acetone and then dried. A puncture wound is made. The first drop of blood is discarded. A fairly large drop (about 3 mm in diameter) of the staining solution is placed over the puncture wound, and the finger is gently squeezed so that a small amount of blood wells up into the drop of staining solution. The correct amount of solution to be placed on the finger and the proportion of blood to be squeezed into it can be learned only with experience. The proportion of blood to stain should be small (about 1:5) so that a well-spread preparation, not overcrowded with red blood cells, is obtained. The

mixture of blood and stain is immediately transferred to a cover slip, which is then dropped on a slide. Cleanliness of glassware is essential.<sup>6</sup>

The preparation is examined under oil immersion lens, preferably after from fifteen to forty-five minutes to permit complete staining of the platelets and reticulocytes. Counts may be made at any time within two hours. Counts made up to four hours, if the preparations are ringed with petrolatum, are also accurate. Permanent preparations cannot be made with this method. Blood platelets, even those measuring only 1 micron or less in diameter, are easily seen as highly refractile opalescent bodies taking a pale bluish stain. Reticulocytes are well stained, even the slightest degree of granulation and reticulation being easily seen. The rapid motion of some of the reticulocyte granules can easily be followed. White blood cells, which also take the stain, may easily be recognized and counted if desired.

One thousand red blood cells are counted (the microscopic field being cut down if desired by the insertion in the eyepiece of an appropriately perforated paper disk), and the number of platelets and reticulocytes seen during this enumeration is recorded. The *number of reticulocytes* is expressed as a percentage of the total number of red blood cells. The *absolute number of platelets* is obtained by (1) performing a count of the red blood cells, and (2) solving the following equation: red blood count 1,000 platelets per cubic millimeter platelets counted. This is most conveniently done by multiplying the first four figures of the red blood cell count by the number of platelets seen in counting 1,000 red blood cells. Thus, if in counting 1,000 red blood cells, 20 reticulocytes and 200 platelets are seen, and the red blood cell count is 3,000,000 per cubic millimeter, the percentage of reticulocytes is 2, and platelet count is 3,000 times 200, or 600,000 per cubic millimeter.

## RESULTS

The method has been used as a routine in the blood laboratory during the past three years. It has proved simple in its application and easy to teach to technicians and medical students. Particularly satisfactory have been the ease with which the platelets are seen and studied and the obtaining of reticulocyte counts in the same preparation.

## RETICULOCYTES

The reticulocytes as seen with this method are unusually well stained, in fact, far superior to those seen in the "wet" method which was described by me in 1926.<sup>7</sup> Numerous comparison counts of reticulocytes were made by the present method and other methods commonly in use. In each instance, the reticulocyte count by this method was at least as high as with other methods and frequently higher. It was felt that the higher counts obtained were due to the

<sup>6</sup> The use of new slides and cover slips is essential. It is advisable to keep them from one to three days in a cleaning solution of sulphuric acid, U. S. P., and potassium bichromate, after which they are thoroughly rinsed in water and kept in an 80 per cent solution of alcohol ready for drying.

<sup>7</sup> Dameshek, W. The Reticulated Red Cells—Their Clinical Significance, Boston M. & S. J. **194** 659 (April 29) 1926.

ease with which even the slightest degree of reticulation could be studied. The last stage in reticulation, the highly refractile granule described by Isaacs<sup>8</sup> could readily be determined. Although Heath and Daland<sup>9</sup> recently reported that a large number of substances, among them sucrose (a constituent of our diluting solution), inhibited the staining of reticulocytes, it was impossible to demonstrate such inhibition in the present study.

#### BLOOD PLATELETS UNDER NORMAL CONDITIONS

*Morphologic Aspects*—Normally, the platelets vary in size from 0.5 to 2 microns and are round, oval or crescentic. They are highly refractile, apparently "solid" and biconvex, in contrast to the biconcave shape of the red blood cell. The smallest of them appear to have a definite, though slight, motility which may be brownian in type. The edge of the platelet is usually "fuzzy," owing to numerous spinelike processes that protrude at all points about the periphery. These processes frequently become greatly lengthened, especially if the preparation is allowed to stand for an hour or more. When two platelets are seen to float near each other, these elongated processes become entangled, causing the platelets to clump together. This appears to be the mechanism by which agglutination of platelets takes place. At either end of some of the larger platelets a hyaline unstained "ectosarc" is frequently observed. The center of the platelets is usually occupied by blue-staining material arranged in granules and, at times, in larger masses. This is not a constant finding and is usually absent in the smallest platelets. At times, the central stained mass resembles a nucleus. Further observations on the morphology of the blood platelets are being made.

*Quantitative Aspects*—One hundred platelet counts on supposedly normal persons with normal hemoglobin and red blood cell count were made. Fifty-two men and forty-eight women were first studied. When the results were plotted, the curve for men showed a normal frequency (chart 1), whereas that for women was irregular.

The mean blood platelet count found for men was 716,000 per cubic millimeter, the median count, 710,000 per cubic millimeter. Fifty-five per cent of the counts were between 600,000 and 800,000 per cubic millimeter, and 84 per cent between 500,000 and 900,000 per cubic millimeter. The normal range for men is probably represented by the latter figures.

<sup>8</sup> Isaacs, R. The Refractive Granule Red Blood Corpuscle. Its Behavior and Significance, *Anat. Rec.* **29**: 299, 1925.

<sup>9</sup> Heath, C. W., and Daland, G. A. Staining of Reticulocytes by Brilliant Cresyl Blue. Influence of Solutions of Substances, *Arch. Int. Med.* **48**: 133 (July) 1931.

Since the frequency curve for presumably normal women selected at random was irregular, it was felt that some variable factor previously ignored might be present. Because of the well known relationship between blood platelets and hemorrhage, the possibility that the

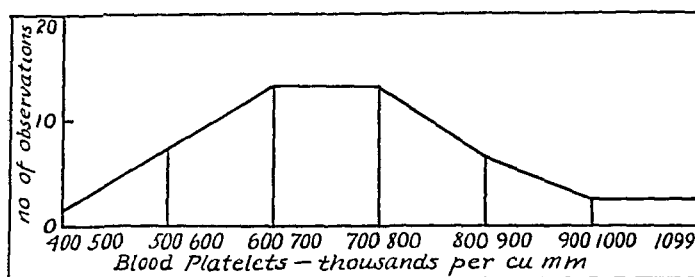


Chart 1—The range of blood platelet counts in normal men

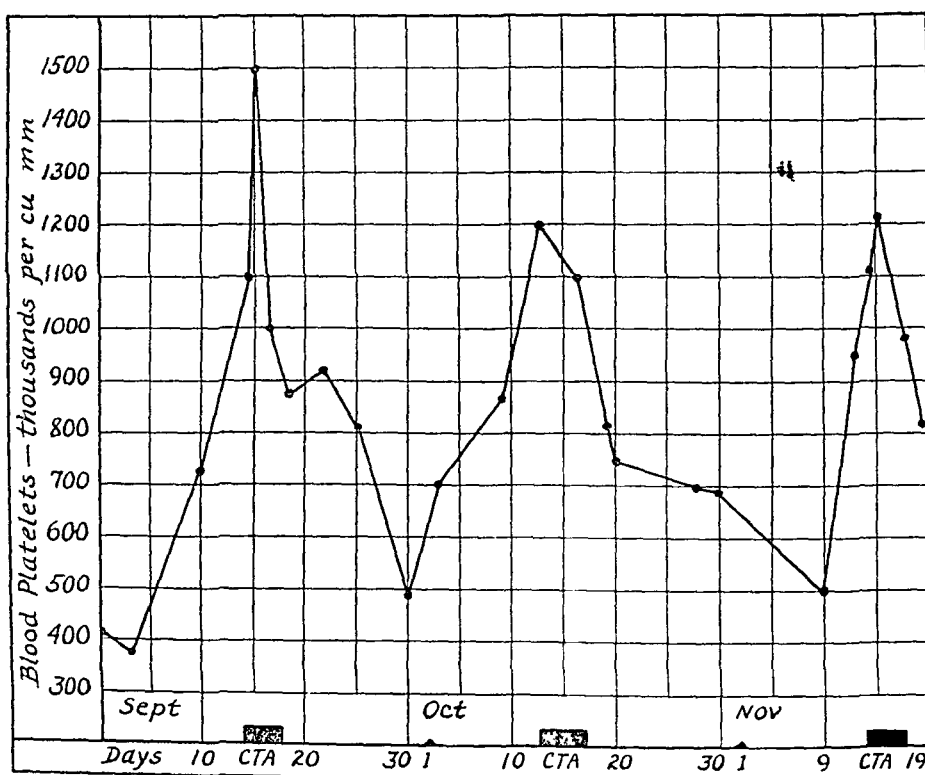


Chart 2—A G, variations in blood platelet count with menstruation, CTA, menstrual flow

menstrual cycle might have some influence on the blood platelet count immediately suggested itself. A series of observations was accordingly made on a small group of normal women at frequent intervals. It was soon found that the counts varied markedly with the menstrual cycle (charts 2, 3 and 4), becoming extremely high on the first day of the period remaining elevated for from three to five days and then

gradually becoming depressed to a fairly constant intermenstrual figure, which varied with the individual subject. On the appearance of the menses, there was always a sudden and marked rise in the blood platelet count, figures of from 1,000,000 to 1,500,000 being usual. The peak of the count was usually reached on the second or third day, after which there was a gradual decline to the intermenstrual level. As comparable controls, frequent platelet counts made on a small group of normal men and on a few nonmenstruating women showed little or no variation from count to count.

Further study of the platelet counts in women is now in progress. At present, normal and mean figures for women cannot be given. However, if one takes the fairly constant intermenstrual figures as representing the normal blood platelet count, the range at this time is usually between 400,000 and 600,000 per cubic millimeter. These

TABLE 1—*Average Number of Blood Platelets Per Cubic Millimeter in Normal Persons as Determined by Various Methods*

Direct Methods		Indirect Methods	
Wright and Kinnicutt <sup>1</sup>	297,000	Fonio <sup>3</sup>	234,000
Buckman and Hallisey <sup>2</sup>	300,000	Pratt (J A M A 45 1999 [Dec 30] 1905)	469,000
Casey and Helmer (Proc Soc Exper Biol & Med 27 665, 1930, 28 523, 1931)	536,000	Olef <sup>5</sup>	619,000

figures probably represent the normal range in women, the menstrual cycle being set aside.

It is probably better to cite normal ranges both in men and in women than to give average figures for a mixed group, as is usually done in most of the published papers. Average normal platelet counts as reported by other investigators are usually lower than with this method, although with his careful indirect technic, Olef has obtained counts in the same range. The normal platelet counts as determined by other methods are given in table 1.

The blood platelet count as determined by this method was compared in about two thousand instances with that determined by the direct method of Buckman and Hallisey. The normal range with the latter method is from 200,000 to 400,000 per cubic millimeter. Higher counts were always obtained with the present method, and usually the counts were twice as high. It was felt that these higher counts were probably more accurate, since they represented the finding of a larger number of platelets per unit of number of red blood cells than with the other method. The implication is present that when direct methods are used, not all of the platelets are counted.

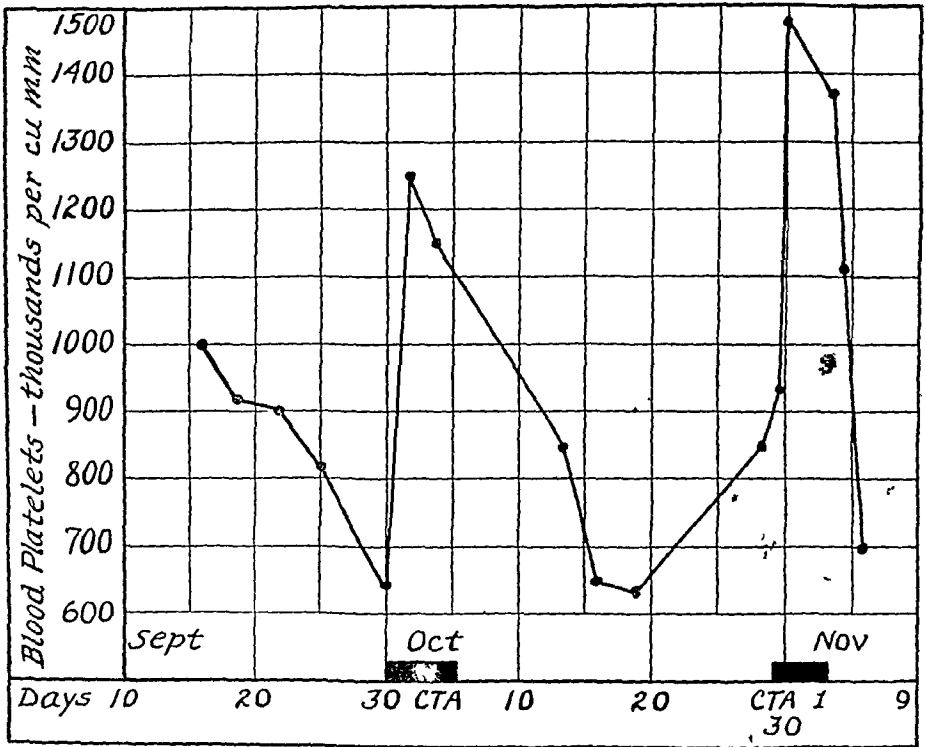


Chart 3—*CD*, variations in blood platelet count with menstruation, *CTA*, menstrual flow

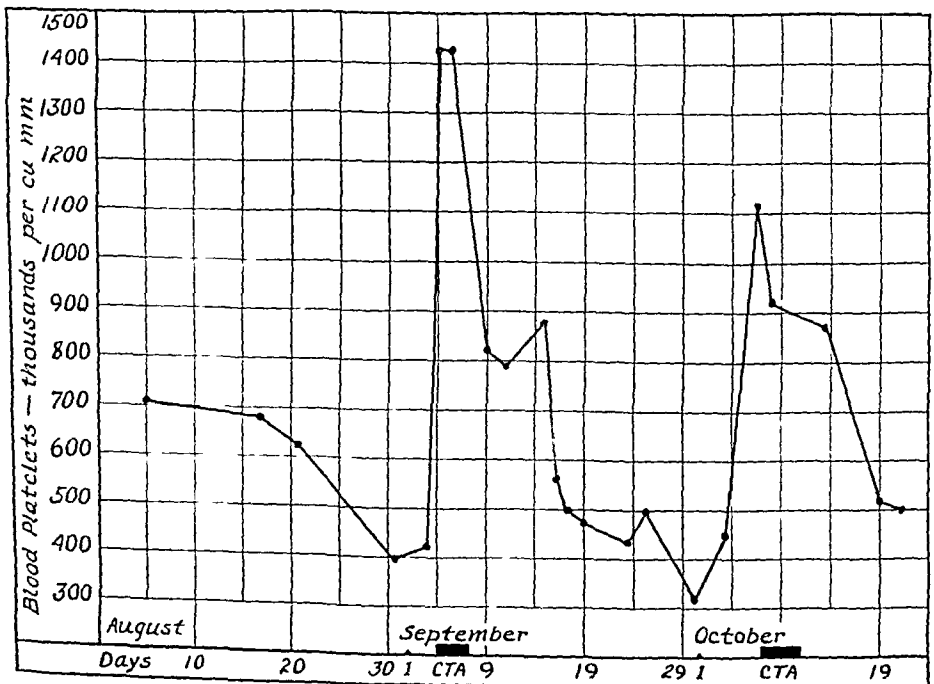


Chart 4—*SG*, variations in blood platelet count with menstruation, *CTA*, menstrual flow

*Accuracy of the Method*—Various procedures were used to check the accuracy of the method previously outlined. These are as follows:

(A) Comparison of Blood Platelet Counts Obtained in Different Preparations of the Same Blood and in Different Fields of the Same Preparation. At times, as seen from table 2, there was rather marked variation in the count of the blood platelets in different parts of the same preparation, the difference being possibly as great as 70,000 per cubic millimeter. This was in all probability due to the unequal distribution of the blood platelets, which at times took place. Absolute cleanliness of glassware is essential in preventing this variation. In the presence of a normal erythrocyte count, a difference in 10 platelets per thousand red blood cells causes a difference in the platelet count of 50,000 per cubic millimeter. The distribution of the blood platelets should therefore be approximately equal throughout the preparation. It is my custom always to make at least two preparations and count different parts of

TABLE 2—Comparison of Platelet Counts in Different Preparations of Same Blood and Different Fields of Same Preparation

	Red Blood Cells (Millions)	Upper Half "A" (Thousands)	Lower Half "A" (Thousands)	Upper Half "B" (Thousands)	Lower Half "B" (Thousands)
J A	5.40	818	838	868	812
S G	5.01	554	574	578	592
R L	4.33	468	406	438	428
B S	5.64	804	778	826	850
E N	1.75	198	174	190	186

the same preparation, obtaining thus an average count of the platelets per thousand red blood cells. If one preparation shows an uneven distribution of the blood platelets, it is discarded, only the satisfactory one being used.

The error in the technic is probably not more than 70,000 per cubic millimeter (about 7 per cent) when the erythrocyte count is high and not more than from 10,000 to 20,000 when the count of the red blood cells and blood platelets is much reduced. With perfection in technic, the percentage of error may further be reduced.

(B) Comparison of Leukocyte Counts by Direct and Indirect Methods. Before blood-counting pipet and hemacytometers were devised, the number of leukocytes was routinely compared with a large number of red blood cells in stained or unstained smears. Normal and abnormal proportions were thus determined. At present, however, the direct method of counting white blood cells in the hemacytometer is universally accepted as accurate. It was felt that the old indirect method could be applied to white blood cell counting and that both methods should give comparable results, especially since there is no error due



to clumping of leukocytes in the pipet (direct method) A comparison of these two methods might therefore be utilized to check the accuracy of the indirect platelet method, especially in patients with high leukocyte counts The aforementioned technic for the enumeration of the blood platelets was accordingly used, the white blood cells being counted in the same preparation A few of these results are given in table 3

As was expected, only little variation was found between the leukocyte count as determined by the undoubtedly accurate pipet method and that obtained in the indirect fashion used to obtain counts of the platelets On the other hand, there was much irregularity and wide differences between the methods used for the enumeration of the blood platelets, owing, in all probability, to the reasons already enumerated

TABLE 3—*Comparison of Leukocyte Counts by Direct and Indirect Methods*

		Red Blood Cells (Millions)	White Blood Cells (Thousands) Pipet Method	White Blood Cells (Thousands) Author's Method	Blood Platelets (Thousands) Author's Method	Blood Platelets (Thousands) Buckman and Hallisey Pipet Method
P A	Acute myelogenous leukemia	2.96	275	296	186	66
		2.88	236	252	178	66
		2.22	248	282	99	68
		2.23	324	312	145	70
		1.88	482	510	54	39
H L	Chronic lymphatic leukemia	2.40	180	196	132	110
		2.67	208	252	235	208
		2.94	318	312	238	102
		2.76	172	196	195	102
		2.78	146	152	222	120
		2.83	108	106	228	106
		2.65	52	68	216	114
		3.17	64	68	263	180
E H	Ulcerative colitis	4.16	25	24	807	404
		3.88	17	17	788	326

(C) Correlation with Clinical Data This new method of platelet counting, by its accuracy, has permitted careful study of a large group of pathologic conditions, and these findings will be elaborated on in a later communication It may be said that in certain diseases in which there was either progressive decrease or increase in the blood platelets, there was exact correlation with the progress of the disease

#### SUMMARY AND CONCLUSIONS

1 An indirect method for the simultaneous enumeration of the blood platelets and reticulocytes is described It depends on the use of an isotonic, anticoagulating solution containing the "vital" dye brilliant cresyl blue The platelets are examined under oil immersion lens Reticulocytes are well stained and are counted simultaneously with the platelets

2 This method has the following advantages (a) It is simple (b) It is accurate (c) It permits accurate recognition of individual platelets and reticulocytes and study of their morphologic aspects (d) It combines in one preparation two hematologic methods platelet counting and reticulocyte counting

3 Normally, there is slight variation in the size and shape of the blood platelets

4 The normal blood platelet count with this method in men ranges from 500,000 to 900,000 per cubic millimeter The normal count in women is made uncertain by the complicating presence of the menstrual cycle The intermenstrual range is from 400,000 to 800,000 per cubic millimeter

5 Various procedures to check the accuracy of the method were undertaken The experimental error is probably not greater than 70,000 per cubic millimeter when the erythrocyte count is normal and not more than 10,000 per cubic millimeter when the erythrocyte and blood platelet counts are very low

# KIDNEY WEIGHT, BODY SIZE AND RENAL FUNCTION

EATON M. MacKAY, M.D.

LA JOLLA, CALIF

In 1916, Addis<sup>1</sup> introduced the determination of the ratio  $\frac{\text{urine urea rate}}{\text{blood urea concentration}}$  under certain standard conditions as a measure of the amount of functioning renal tissue. The adequacy of this ratio as measured under the standard conditions for this purpose was demonstrated in a number of ways. It is a reasonable measure of renal function,<sup>2</sup> the variation in "experimental nephritis" was found<sup>3</sup> to agree well with the structural changes in the kidneys, and the compensatory renal hypertrophy as measured by the ratio coincided with the anatomic measurements.<sup>4</sup> Lastly, it was shown<sup>5</sup> that in rabbits there existed a linear relationship between the magnitude of the ratio and the weight of the kidneys, an observation since confirmed for the rat<sup>6</sup> and the dog.<sup>7</sup> Taylor, Drury and Addis<sup>5</sup> found that in rabbits the kidney weight varied directly in proportion to the body surface and bore a more constant relation to this figure than to any other measure of body size. This observation along with the similar finding by Stewart<sup>8</sup> in the dog and the more constant relation of the ratio of urea excretion to body surface than to other measurements of body size in man led Addis<sup>9</sup> to assume a direct relationship between kidney weight and body surface and to correct his ratio for urea excretion, when used for measuring the amount of functioning renal tissue in

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From the Scripps Metabolic Clinic

1 (a) Addis, T., and Watanabe, C. K. *J. Biol. Chem.* **28** 251, 1916. (b) Addis, T. *J. Urol.* **1** 263, 1917, (c) Renal Function and the Amount of Functioning Tissue, *Arch. Int. Med.* **30** 378 (Sept.) 1922.

2 Addis, T. *Am. J. M. Sc.* **176** 624, 1928.

3 Watanabe, C. K., Oliver, J., and Addis, T. *J. Exper. Med.* **28** 359 (Sept.) 1918.

4 (a) Addis, T., Myers, B. A., and Oliver, J. The Regulation of Renal Activity, *Arch. Int. Med.* **34** 243 (Aug.) 1924. (b) Oliver, J. The Regulation of Renal Activity, *Arch. Int. Med.* **34** 258 (Aug.) 1924.

5 Taylor, F. B., Drury, D. R., and Addis, T. *Am. J. Physiol.* **65** 55, 1923.

6 MacKay, E. M., and Raulston, B. O. *J. Exper. Med.* **53** 109, 1931.

7 MacKay, E. M. *Am. J. Physiol.* **100** 402, 1932.

8 Stewart, J. N. *Am. J. Physiol.* **58** 45, 1921.

9 Addis (footnote 2) Addis, Myers and Oliver (footnote 4a)

patients, according to the body surface of the subject. Additional evidence in support of this practice has been offered by McIntosh, Moller and Van Slyke<sup>10</sup>. It has been indicated elsewhere<sup>11</sup> that the expected kidney weight could be predicted in man most accurately from the surface area as a measure of body size. However, the evidence for this statement was not presented, and it seems desirable to demonstrate that body surface is the best reference standard for renal weight in man.

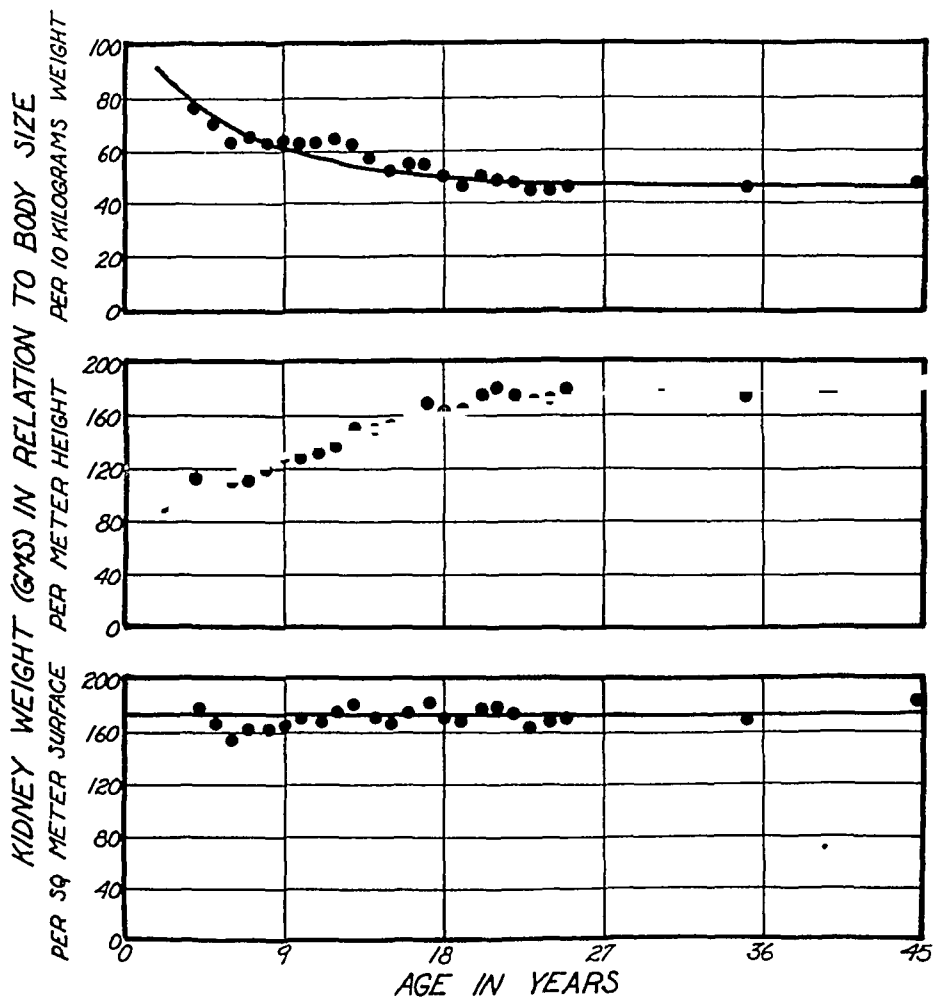


Chart 1—Weight of kidney in relation to body surface, height and weight, plotted against age

#### KIDNEY WEIGHT IN RELATION TO BODY SIZE

The figures quoted by Vierordt<sup>12</sup> for body weight, height and kidney weight in relation to age were used. Body surface was calculated

<sup>10</sup> McIntosh, J. F., Moller, E., and Van Slyke, D. D. *J. Clin. Investigation* 6: 467, 1929.

<sup>11</sup> MacKay, E. M., and MacKay, L. L. *J. Clin. Investigation* 4: 127, 1927.

<sup>12</sup> Vierordt, H. *Anatomische, physiologische und physikalische Daten und Tabellen*, ed. 3, Jena, Gustav Fischer, 1906, pp. 8, 22 and 36.

by the usual formula of DuBois<sup>11</sup> In chart 1 kidney weight in relation to these three measures of body size has been plotted against age In a general way the relationship is similar to that reported for the albino rat<sup>14</sup> The kidney weight in relation to body weight decreases with age and in relation to body length, as might be expected, increases with age The relation of kidney weight to body surface is practically the same at all ages being a direct one This is shown even better

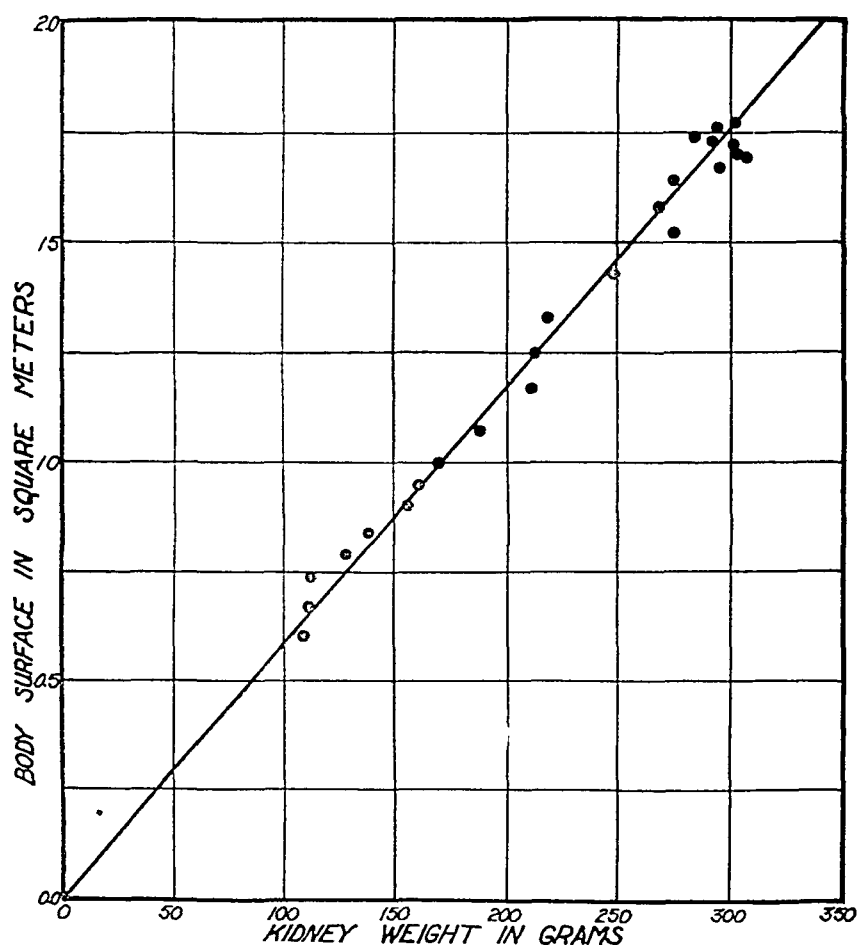


Chart 2—Relation of body surface to kidney weight

in chart 2 It has already been pointed out that a similar relationship exists in the rat<sup>14</sup> the rabbit<sup>5</sup> and the dog<sup>8</sup>

#### KIDNEY WEIGHT IN RELATION TO RENAL FUNCTION

Since kidney weight is directly proportional to body surface it follows that the Addis ratio for urea excretion will likewise be proportional to

<sup>13</sup> DuBois, E. F. Basal Metabolism in Health and Disease, Philadelphia, Lea & Febiger, 1927

<sup>14</sup> MacKav, L. L., and MacKav, E. M. Am J Physiol **83** 191, 1927

kidney weight in man because of the direct relation that has been demonstrated<sup>10</sup> between body surface and the urea ratio. The data of McIntosh, Moller and Van Slyke<sup>10</sup> on the relation between body surface and the high volume urea ratio have been reproduced in chart 3 (*A*) and compared with some new figures (*B*) of our own on a number of children and young adults, all males. From the relationship found in chart 2, the kidney weight has been determined indirectly, and its relation to the urea ratio is shown. This is a direct one.

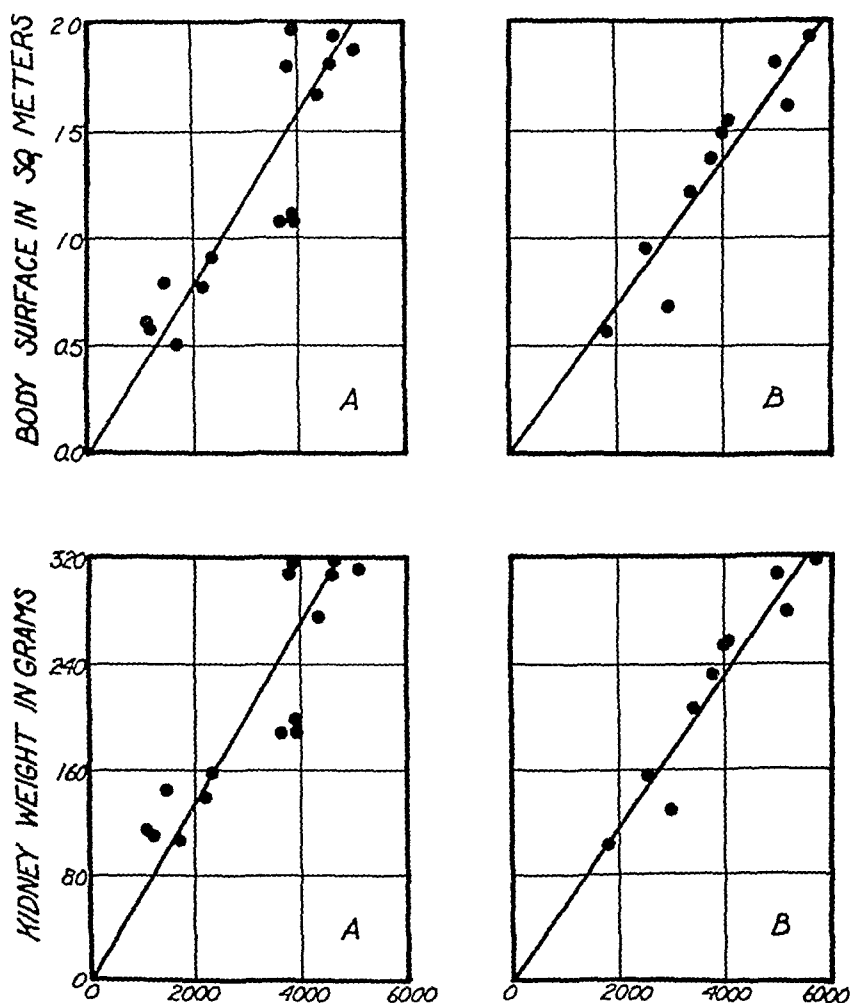


Chart 3—Relation of kidney weight to the urea ratio. Addis ratio  

$$\frac{\text{urine urea rate — mg per hour}}{\text{Blood urea concentration — mg per 100 cc}} \times 100$$

*A* illustrates the data of McIntosh, Moller and Van Slyke and *B*, those of MacKay.

In chart 3 the relation between the body surface and the high volume ratio  $\frac{\text{Mg urine urea per hr}}{\text{Mg urea per cc blood}}$  is somewhat different in the two sets of observations. The average of the figures (*A*) from McIntosh, Moller and Van Slyke<sup>10</sup> is 2,524 cc, while the average of our figures (*B*) is 2,970 cc per square meter of body surface. The only difference in the method of obtaining the two sets rests in the use of an ideal

weight for height in obtaining the body surface of the "A" group while the actual body weight was used for calculation of the "B" group. We have recalculated the "A" figures on the latter basis, but the result is essentially the same. Since the average of these two sets of figures, 2,757, so closely approximates the average of 2,770 cc per square meter found by Addis<sup>15</sup> in 163 observations on 31 young adults, it seems best to retain this figure, which has been the normal standard in Addis' laboratory<sup>16</sup> for many years. From what is known of kidney weight in relation to body surface in animals and to sex it seems probable that the standard for the female should be lower than for the male sex. However, as McIntosh, Moller and Van Slyke<sup>10</sup> have noted, the difference is probably immaterial for practical purposes, in any case, data sufficient to make the distinction are not available.

#### SUMMARY

In man renal function as measured by the ratio  $\frac{\text{urine urea rate}}{\text{blood urea concentration}}$  under certain standard conditions and kidney weight are both directly proportional to the body surface

<sup>15</sup> Addis (footnotes 1 b 2 and 4)

<sup>16</sup> McIntosh, Moller and Van Slyke (footnote 10) Volhard, F. Nieren und ableitende Harnwege, Berlin, Julius Springer, 1931, p 155

# NONTROPICAL SPRUE WITH DUODENAL INVOLVEMENT AND TETANY

ROBERT B RADL, M D

AND

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MINNEAPOLIS

It is easy to distinguish several indirect effects of the introduction of the liver therapy in pernicious anemia by Minot and Murphy. The differential diagnosis between pernicious anemia and other obscure and severe anemias has been sharpened. The rôle of the gastro-intestinal tract in the pathogenesis of anemias has been stressed and the nutritional factor more strongly emphasized than during the preceding ten years of high tide of interest in vitamins.

The following study of a single case is presented because of the anemia, for some time looked on as pernicious, because of the sprue-like disturbance of intestinal absorption and motility, because of the tetany resulting from this disturbance, and finally because of marked duodenal changes and their relation to the other symptoms.

## REPORT OF A CASE

*History*—Mr A J, aged 41, born in Wisconsin of Swedish extraction, is an unmarried farmer. He has never been away from the north central region of the United States. Though in general his past health has been good, he was never a robust child. There is nothing to indicate any unusual dietary mismanagement. He had pneumonia at the age of 4. At 10, his knee joints were stiff, swollen and painful, but there was no fever, he was not confined to bed, and there were no sequelae. Roughness and furrowing of the finger-nails have been noted for about seventeen years. Bilateral incomplete inguinal hernia has been noted for three years.

*First Admission to Hospital (July, 1928)*—The first symptom of the present illness was soreness of the tongue, which began insidiously about eight years before his admission to the hospital. It was intermittent and severe enough to cause him to select bland foods. The first gastro-intestinal symptoms occurred about six years later, when a change in the character of the stools was observed. He noted an urge to defecate about 3 or 4 a m. The stools were larger than normal, semi-solid, normal in color but not frothy, nor was blood or mucus ever noticed. His general condition remained stationary for about a year. Then the stools gradually increased in number, there were usually two movements early each morning. Defecation did not afford the usual sensation of relief, and there was abdominal

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discomfort The appetite remained undisturbed, but the patient felt fatigued and lost about 10 Kg in weight There was no nausea or vomiting He had felt numbness and tingling of hands and feet for about four years more or less constantly

*Physical Examination (1928)* —The patient did not appear acutely ill He was poorly developed, of apparently subnormal constitution His posture was drooping, his stature undersized, his shoulders narrow (fig 1) He weighed 49 Kg and was 157 cm in height Other recorded measurements were crown to sym-

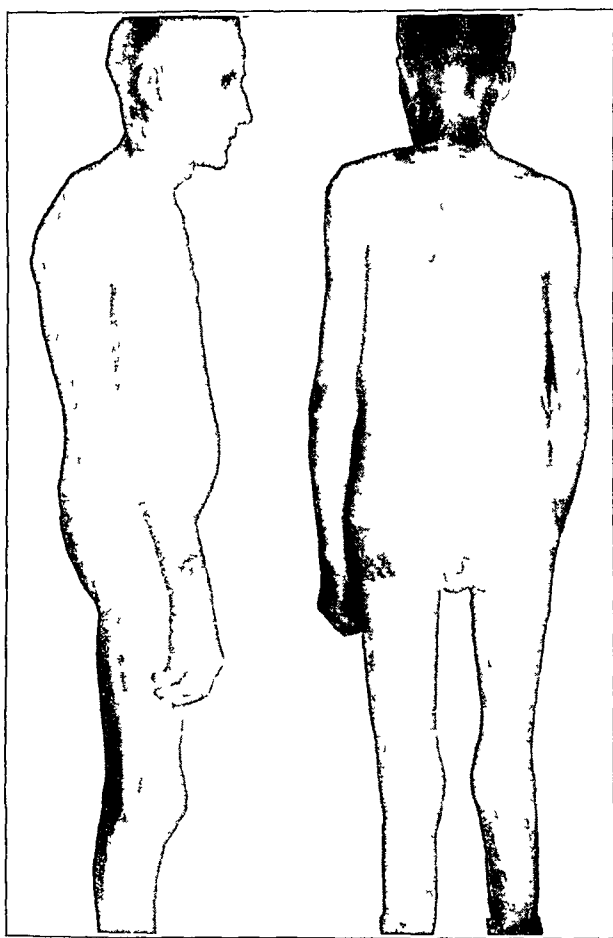


Fig 1—The bodily habitus of the patient

physis, 77 cm, symphysis to floor, 80 cm, chest on inspiration, 82 cm, and on expiration, 76 cm, waist, 76 cm, iliac crests, 79 cm, span of arms, 165 cm There were seven upper and six lower teeth present Onychia gryposis was present in six finger-nails He responded sluggishly to questions and talked listlessly and slowly The temperature was normal, the pulse rate, from 60 to 90 The skin was dry and cool, there were no areas of pigmentation The hair was dry, but normal in distribution The papillae of the tongue were markedly atrophic, but no aphthae or ulcerations were present The tonsils were submerged and a few cervical nodes slightly enlarged The thyroid gland was not palpable The heart and lungs were normal, except for a faint, systolic murmur heard over the aortic area The blood pressure was 100 systolic and 70 diastolic No other

abnormalities were noted, except evidence of bilateral inguinal hernias. All reflexes were normal. The joint position sense and vibration sense were normal.

*Laboratory Data*—The result of a Wassermann test of the blood was negative. The urine was normal on various occasions. An Ewald meal showed no free hydrochloric acid present. The stools were light yellow and contained undigested particles of food. No blood, ova or parasites were found. The results of roentgen examination of the stomach and duodenum are illustrated in figure 2, they are discussed in later paragraphs. The blood count (Aug 1, 1928) revealed 2,870,000 erythrocytes and 5,000 leukocytes, the hemoglobin content was 64 per cent (Sahli). The color index was 1.14. There were moderate poikilocytosis and marked anisocytosis with many macrocytes. After liver therapy (2 capsules of liver extract four times daily) the following improvement occurred. On October 22 to 28, the red cell count was 5,700,000, the hemoglobin content, 85 per cent.

*Clinical Course*—The patient felt better as a result of the administration of liver extract. He gained 5 Kg in weight, the blood improved, but the bulky stools persisted. He was discharged on Sept 13, 1928, with a diagnosis of pernicious anemia without neurologic changes.

*Second Admission (Feb 17, 1930)*—The patient had continued to feel well. He claimed to have taken one-half pound (227 Gm) of liver daily for about a year. In September, 1929, the taking of liver was discontinued because of distress, fulness or pressure in the epigastrium. The epigastric pain was partially relieved by eating. The gastric symptoms became worse and were aggravated by fried foods or coarse vegetables. Nausea and vomiting had occurred intermittently following December, 1929. Vomiting and belching relieved the distress. The early morning bowel movements persisted, the number of stools varying from two to five. They were of the same character as described in the previous paragraphs.

*Physical Examination*—No changes were revealed except that a vague mass was palpated 3 cm below the right costal margin. It was not tender or movable. The gastric secretion was tested after 0.5 mg of histamine had been given, free hydrochloric acid was present with Gunzburg's test after forty minutes, but not after twenty or sixty minutes. Roentgen examination (Feb 21, 1930, fig 2 b) showed a dilated stomach and duodenal stenosis (see later paragraphs). The blood pressure was 94 systolic and 64 diastolic. The response to medical treatment for peptic ulcer was poor, and on March 10, 1930, a typical posterior gastroenterostomy was performed with the anastomosis made transverse along the greater curvature (Dr L. W. Tasche). The findings at operation were described as follows. A large duodenal ulcer extended over almost the entire first portion of the duodenum, narrowing it very much. The second portion of the duodenum seemed normal. The lesser peritoneal sac showed signs of recent inflammation by adhesions.

Convalescence was uneventful. The patient was discharged on March 31, 1930, with the diagnosis recorded as duodenal stenosis with partial obstruction.

*Third Admission (June 17, 1930)*—Although the patient had gained slightly in weight he had not improved much. There had been no vomiting, but the loose bowel movements persisted. In May he had an attack of severe, painful tetanic contracture and flexion of the forearms, hands and legs below the knees. The fingers were flexed over the adducted thumb. Similar attacks recurred at intervals of about five days lasting from thirty minutes to three hours. Slight edema of the legs was noted. The edema was unaffected by posture.

*Physical Examination*—There were no new findings, except that Chvostek's and Trousseau's signs were present. The abdominal and deep reflexes were absent,

except during attacks of tetany, when they were present and increased over the normal in intensity. There was slight pitting edema of the lower legs. No studies of the blood calcium were carried out on this admission. By the administration of calcium lactate and parathyroid extract the attacks of tetany were controlled. The patient's weight increased from 38 to 41 Kg, while his edema diminished. His appetite was fair, the addition of dilute hydrochloric acid had no apparent effect. He was discharged on Aug 6, 1930.

*Fourth Admission (Sept 17, 1930)*—About two weeks before the fourth admission, tetany recurred. Attacks came on daily and lasted from one-half to one hour. The edema of the legs increased markedly, especially that in the left leg. There was considerable abdominal distention. The blood pressure was from 96 to 100 systolic and from 60 to 70 diastolic. The stools were unchanged in character, but had increased in number to five or more daily. The stool was bulky, semisolid and light yellow, weighing on the average 16 ounces (475 Gm), they were never frothy. When the stools were frequent, they tended to be watery. Microscopic examination showed undigested particles of food and globules of fat. Stercobilin was present, blood was never found.

Analysis of the gastric juice showed hydrochloric acid to be present on one occasion after injection of histamine and absent on another. The total acidity varied between 14 and 36, the total chlorides in the first and the last tests with histamine were as given in the table.

*Total Chlorides of Gastric Juice, Mg per Hundred Cubic Centimeters*

	Before Gastro Enterostomy (2/19/30)	After Gastro Enterostomy (12/16/30)
Fasting	228	327
20 min	304	246
40 min	339	327
60 min	382	331

Two separate determinations of the basal metabolic rate, when no tetanic cramps were present, gave values of  $-19$  and  $-21$ . An earlier determination, disturbed by continuous cramps, had given a value of  $+30$ . A dextrose tolerance test gave a normal curve.

The lowest value determined for the serum calcium was 5 mg per hundred cubic centimeters. With sufficient calcium lactate (12 Gm daily) and parathormone (10 to 30 units daily) given to keep the patient free from tetany, the serum calcium was usually found between 7 and 9.8 mg. The inorganic serum phosphorus was 4.2 mg, while the calcium was 7 mg.

The plasma proteins (May 4, 1931) were 6.48 per cent total protein, 3.16 per cent albumin and 3.32 per cent total globulin. The globulin fraction was composed as follows: fibrinogen 0.72 per cent, euglobulin, 0.56 per cent, pseudoglobulin I, 1.48 per cent, and pseudoglobulin II, 0.56 per cent. The blood nonprotein nitrogen was 35 mg per hundred cubic centimeters.

*Roentgen Observations*—The roentgen studies carried out during the course of our observations are summarized by Dr. Leo Rigler as follows:

The first examination (July 13, 1928) revealed some hyperperistalsis, and at times, spasticity of the pylorus. Some relaxation of the pylorus also took place. The duodenal bulb was rather small, but normal otherwise. There was a marked narrowing of the second, and to some extent of the third, portion of the duodenum, suggesting some type of stenosis. A diverticulum of the jejunum was also made out.

The next examination (Jan 31, 1930) showed a marked change in the appearance. The stomach was distinctly dilated, and there was marked hyperperistalsis. Marked stenosis of the pylorus was present. The duodenal bulb was extremely small and irregular, and there was marked stenosis of the second and third portions of the duodenum, which had increased considerably since the last examination. The appearance suggested a rather extensive ulcerated process of the duodenum with marked periduodenal adhesions. The diverticulum previously reported was again shown. The third examination (Feb 21, 1930) showed about the same changes. About 80 per cent retention in the stomach was present after six hours. The next examination (March 5, 1930) showed such extreme retention in the stomach that it was impossible to visualize the small bowel.

The next examination (March 24, 1930) showed a well functioning gastro-enterostomy. There was still a small trace of barium passing through the pylorus.

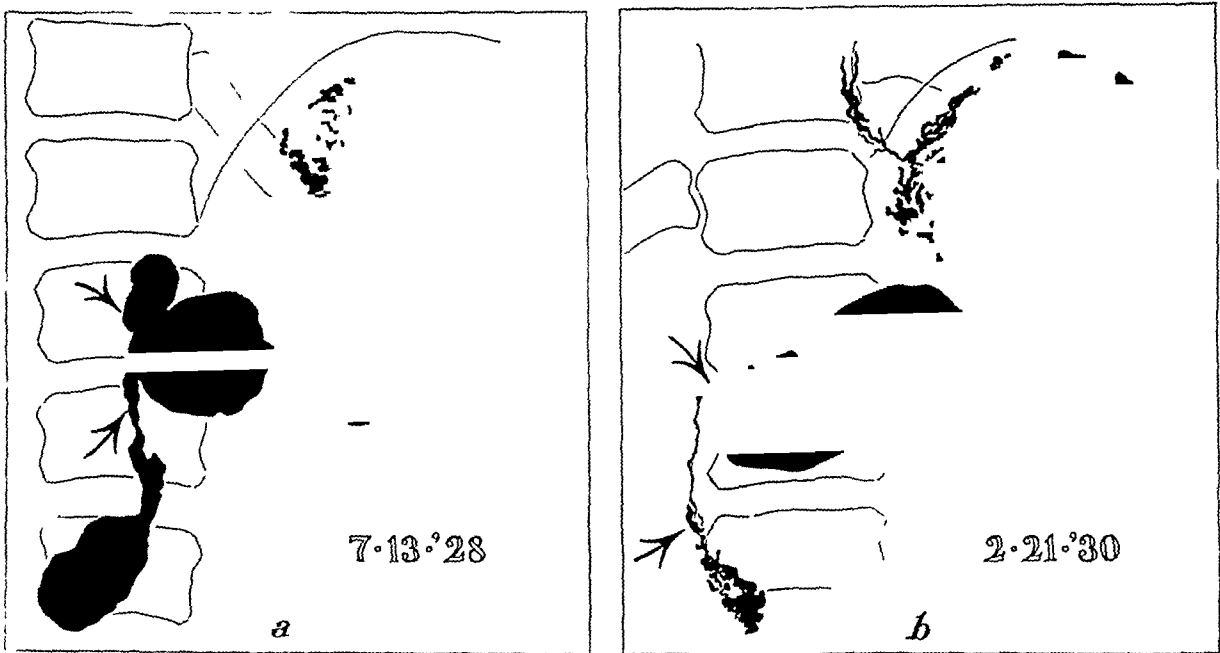


Fig 2—Drawings showing roentgenographic appearance of stomach and duodenum (a) July 13, 1928, and (b) Feb 21, 1930

and duodenum, but these were difficult to visualize. The stomach was reduced in size. The next examination (June 18, 1930) again showed the gastro-enterostomy functioning well, with no other evidence of a pathologic condition.

The final examination (Nov 19, 1930) showed the gastro-enterostomy functioning fairly well, but much more barium passing through the pylorus. The stenosis of the duodenum previously reported was again shown, and the third portion of the duodenum showed some dilatation. There was also some regurgitation from the third portion of the duodenum into the pylorus.

Repeated examinations of the colon were made. These showed extreme redundancy of the colon, but no other evidence of a pathologic condition. Examination of the pelvis, skull and femur on Oct 24, 1930, showed some decalcification of the pelvis, but this was slight, and the clinical significance of it is questionable. Examination of the gallbladder on Feb 24, 1930, was made. This was not satisfactory, no shadow of the gallbladder could be made out, suggesting that it was not functioning well.

The conclusions were (1) dilated stomach showing hyperperistalsis, (2) stenosis of the pylorus and of the first, second and third portions of the duodenum of extreme degree, with gastric retention, (3) diverticulum of the jejunum, (4) gastro-enterostomy, functioning well, (5) redundancy of the colon, (6) questionable involvement of the gallbladder, and (7) slight decalcification of the pelvis

*The Blood*—The blood never presented a convincing morphologic picture of pernicious anemia. The red cells at first showed moderate anisocytosis with macrocytes, normocytes and microcytes. The macrocytes were hyperchromatic, and some of the normocytes and microcytes were hypochromatic. In the blood smear, the color index appeared to be only slightly above 1. In smears taken on later admissions, there was a predominance of macrocytes, so that the color index appeared to be increased considerably, and a normal amount of polychromatophilia was present. There was always from a moderate to a slight amount of poikilocytosis. Occasionally basophilic stippling was seen. No nucleated red cells were present.

The neutrophils were normal in size and percentage. The nuclei were moderately shifted to the right (from 3 to 8 lobes), and the granulation was uneven in size and tended to be basophilic (toxic granulation). An occasional neutrophil was slightly larger than normal, but none of them had the large, even pink granulation seen in the neutrophils of pernicious anemia.

The lymphocytes were not increased in percentage. They were chiefly the large lymphocytes with large azure granules. The monocytes were reduced in percentage, being almost entirely absent in the early smears, but reaching a low normal percentage in the later smears. They presented toxic changes. The platelets were reduced in number in the early smears, but later appeared to be about normal in number and larger in size.

The blood picture remained fairly constant throughout, with the exception of the increase in the size of the red cells, the slight increase in the amount of polychromatophilia, and the variation in the number and size of the platelets.

Since the blood smears contained the toxic type of neutrophils rather than the neutrophils of pernicious anemia, and since the percentage of neutrophils was normal, we were not dealing with a true picture of pernicious anemia.

*Response to Therapy*—On Aug. 1, 1928, the patient's blood had a hemoglobin content of 64 per cent (Sahli), the red cell count was 2,870,000, and the white cell count, 4,950. After forty-three days on liver therapy (a concentrated liver preparation, 8 capsules daily) the hemoglobin content was 91 per cent, the red cell count, 5,650,000. He was discharged and told to eat one-half pound of raw liver daily. He continued taking liver, alternating raw liver and liver extract until September, 1929, when he began to take it irregularly. During this year on liver, his hemoglobin remained at a high level, 79 to 85 per cent, but the red cell count ranged from 3,400,000 to 4,400,000.

Following the second admission, he was given raw linseed oil (5 cc three times daily) for eleven days. There was a slight increase in the hemoglobin, from 89 to 99 per cent, and a slight change in the red cell count, from 3,410,000 to 3,980,000. The reticulocyte count ranged from 0 to 1.6 per cent.

Following the gastro-enterostomy there was no treatment for four months. Then over a period of thirty-nine days he was given calcium lactate and parathormone. At the end of this period the hemoglobin content was 63 per cent, the red cell count 3,050,000 and the white cell count 4,200.

On the fourth admission raw linseed oil was tried again in larger dosage (45 cc three times daily). The hemoglobin increased from 73 to 80 per cent. The

red cell count rose from 2,880,000 to 3,390,000, but both dropped again to the original levels. The reticulocyte count varied from 1 to 4.2 per cent.

Iron ammonium citrate (6 Gm daily) was then given with a high caloric, high vitamin diet over a period of twenty-two days, with no appreciable change in the hemoglobin, red cell count or reticulocyte count.

A diet high in protein but low in salt and sugar-free was tried for two weeks. Although there was no significant change in the percentage of hemoglobin or in the number of red cells, the reticulocyte count rose to 4.2 per cent.

A general diet with extra fat, butter, cream and milk was given for two weeks. The reticulocyte count ranged from 2 to 2.5 per cent.

Then liver extract no. 343 (8 vials daily) was given for eighteen days with a diet high in protein, but low in sugar and fat. The hemoglobin increased from 82 to 90 per cent, but fell again to 74 per cent. The red cell count increased from 2,820,000 to 3,480,000, but fell to 2,990,000. The reticulocyte count varied from 2 to 3.6 per cent.

The same diet was maintained, but 150 Gm of raw calves' liver was substituted for the liver extract. The hemoglobin gradually rose to 90 per cent, and the red cell count reached 4,630,000. The reticulocyte count varied from 1.4 to 3.4 per cent.

#### COMMENT

The first symptom was sore tongue, present eight years prior to the first observation. When the patient was first seen, the anemia was not sufficiently marked to produce a typical morphologic picture of pernicious anemia, while the improvement following medication with liver extract was compatible with such a diagnosis. The patient's appearance, one of general debility (fig 1), was much against pernicious anemia. There were reasons why adequate consideration was not given to the roentgen evidence of a pathologic duodenum. There were not the usual subjective symptoms of duodenal ulcer, neither were the films characteristic of such a condition, the abnormalities of the stools of two years' duration seemed compatible with pernicious anemia, as was the achlorhydria in the Ewald meal, the latter compatible also with duodenal ulcer. The absence of spinal cord symptoms was not incompatible with pernicious anemia of moderate severity.

The rapid development of the duodenal lesion into a stenosis of considerable length dominated the second hospitalization, while the anemia remained much the same as when the patient was first seen. Again it is noted that the pain and discomfort associated with the duodenal changes were slight up to the time when symptoms of retention developed. Symptoms of earlier perforation could not be elicited. Though there was no indication for opening the duodenum during the operation, the observations made it possible with moderate certainty to rule out malignant tumor, tuberculosis and syphilis.

With the facilities for adequate nutrition mechanically improved by a well functioning gastro-enterostomy, the patient nevertheless grew worse, a definite condition of deficiency being signaled by the début

of tetany. Interest in this condition lately has been greatly intensified, and a variety of causes have been described. Its occurrence in sprue is often referred to while mention of its occurrence in cases of pyloric stenosis with dilatation of the stomach and copious or prolonged vomiting is becoming very rare. Association of its occurrence with pancreatic disease recently has been placed in abeyance by British writers (Linder and Harris<sup>1</sup>), Berglund, however, in a case seen in consultation, saw severe tetany in combination with the typical symptoms of pancreatic insufficiency, the latter having developed acutely immediately after an operation for perforated duodenal ulcer, in the course of the operation, the pancreatic duct had been caught and closed by a suture. During his sojourn in Peiping, Berglund also observed tetany in an otherwise normal young Chinese mother, in whom the drain on the calcium supply produced by lactation was sufficient to precipitate tetany. For all these forms it appears certain "that the tetany has its basis in a deficiency of calcium" (Linder and Harris<sup>2</sup>), of which a low level of the serum calcium is an indication.

On the basis of the roentgenogram (fig 2b) of our patient, one might consider the possibility of secondary occlusion of the pancreatic ducts. The abnormality of the stools is hardly pronounced enough to correspond to the typical syndrome of pancreatic exclusion, the bulky and frequent stools were present a long time before the duodenal condition was marked, and the aggravation of the condition has been very gradual. An interpretation nearer at hand is that of nontropical sprue. The number of such cases that have been reported both from Europe and America is sufficient to have made the condition well recognized, some cases closely correspond to the picture of tropical sprue, others are less well defined. The following symptoms and signs may be said to constitute a typical picture of the moderately advanced case: dyspepsia, flatulence, capricious appetite, constipation alternating with voluminous liquid or semiliquid stools, which are often foamy and light yellow, glossitis or stomatitis, anemia of pernicious type, muscle cramps, loss of weight, low blood pressure and mental depression. Secondary symptoms may be present, such as edema of the extremities and tetany with low blood calcium.

The following detailed observations on our patient deserve brief comment. *Monilia pinoyi* was isolated from the stools and identified by Dr. A. T. Henrici of the department of bacteriology. In regard to etiology, little significance is placed on this finding. It is commonly believed that the incomplete digestion and the fermentation merely provide favorable conditions for its growth.

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1 Linder, G., and Harris, C. F. *Quart J Med* 23: 195, 1930.

The general debility is expressed in many ways besides in the exterior of the patient. That there are numerous possibilities for faulty intestinal absorption does not have to be emphasized. The patient for more than a year has had recurrent superficial ulcers of the cornea. Xerophthalmia is not present, neither have the ulcers shown the same dangerous tendency to perforate as did the instances of keratomalacia frequently observed by Pillat in Peiping among adult Chinese suffering from a deficiency of vitamin A. There is no cataract, which frequently is present in parathyroid tetany.

The basal metabolic rate is below the range of normal variability. Of interest is the degree of its elevation, from  $-20$  to  $+30$  during the active state of tetany.

Contrasted against the low metabolic rate and the wasted condition of the musculature are the concentrations of the plasma proteins, which are well within normal variability. The fibrinogen is above the normal range and a little more than twice the normal mean. Serum calcium is pathologically low. There is no creatinuria.

The ability to secrete hydrochloric acid is not completely lost; at least not all the time, the secretion, when produced, is minimal. The concentration of total chlorides is below the normal mean as established by Berglund, Johnson and Chang, but well within normal variability, the values fall just within  $-1$ , the standard deviation for their mean. The total chloride values in pernicious anemia the same investigators usually found to be lower than in this patient.

Of special tests for pancreatic secretion, only the digestion of cell nuclei, according to Adolf Schmidt, was carried out. Without vouching for the specificity of the procedure as a test for pancreatic function, we may say that the result was clearcut. Of five small gauze parcels containing sweetbread given to the patient, four were recovered showing the nuclear structures fully preserved, while from the interns who took the test simultaneously only the gauze was recovered. A dextrose tolerance test gave a normal blood sugar curve. Too much significance should not be attached to this finding. The rate of dextrose absorption may have been reduced and may thus have influenced the curve.

The blood in 1928 responded promptly to liver extract, in 1931, poorly, but better to raw liver than to liver extract. Considering the amazing difference recently demonstrated by the Boston group in the amount of active principle needed by mouth and when parenterally administered the poor response in our patient was thought to be due possibly to failure of absorption. Intramuscular administration of liver extract was therefore tried (10 cc of extract no. 343 for eight days), with no response.

Our observations clearly indicate that the anemia responded to raw liver and liver extract but not to iron or to linseed oil.



The general condition has, on the whole, been resistant to different forms of therapy, there has been no improvement similar to that observed by Porter and Rucker<sup>2</sup> after liver extract or by Linder and Harris<sup>1</sup> after restriction of the fat intake. Large doses of viosterol gave no definite improvement. The tetany has not been controlled by diet, large doses of calcium lactate and parathormone are necessary over and over again.<sup>3</sup>

#### SUMMARY

A condition that deserves the diagnosis nontropical sprue has been described, presenting, besides bulky fatty stools, anemia, duodenal stenosis and tetany. Constitutional inferiority is considered a factor of pathogenic importance. The response to different therapeutic procedures was unsatisfactory. Detailed chemical and hematologic studies are reported.

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2 Porter, W. B., and Rucker, J. E. *Am J M Sc* **179** 310, 1930.

3 Our interest being focused on the early diagnosis of nontropical sprue and the possible justification of speaking of mild and abortive forms, we wish to mention a patient under observation at the present time.

A. V. is a white man, aged 33, born in this country. The history is essentially one of having large and frequent stools intermittently for the past eleven months, sore tongue and attacks highly suggestive of tetany. A diet high in carbohydrate produces stools typical of sprue, and the condition is easily checked by a diet low in carbohydrate and low in fat. There is a normal hydrochloric acid content of the gastric juice, there is no anemia. The result of the sweetbread test is normal. But for our interest in sprue and the history of sore tongue and tetany, the condition probably would have been labeled fermentation dyspepsia as conceived by Adolf Schmidt.

# EXPERIMENTAL STUDIES IN GASTRIC PHYSIOLOGY

## EVALUATION OF THE RÔLE OF DUODENAL REGURGITATION IN THE CONTROL OF GASTRIC ACIDITY IN MAN (BOLDYREFF THEORY)

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Since Heidenham's<sup>1</sup> observation that the pure gastric juice in the normal dog was secreted at an acidity of 0.5 to 0.6 per cent hydrochloric acid, and particularly since its confirmation in human beings by Carlson,<sup>2</sup> physiologists have puzzled over the mechanism involved in the reduction of this high acidity to the one ordinarily seen in gastric contents. In general, the many theories evolved to explain the reduction concern themselves with one or the other of two mechanisms (1) neutralization and (2) dilution. Babkin<sup>3</sup> recently gave an excellent résumé of this subject. It is our intention to inquire into only one of these theories, the one that has doubtless enjoyed the greatest popularity. This is the theory developed by Boldyreff and styled by him "the self-regulation of gastric acidity." Briefly, it contends that the small intestine cannot tolerate an acid stronger than from 0.1 to 0.15 per cent hydrochloric acid. In order to render the gastric acid acceptable to the small intestine, it must be reduced from an approximate concentration of 0.5 to 0.15 per cent. Boldyreff<sup>4</sup> stated that the strong acid, passing from the stomach into the intestine, provokes an abundant secretion, chiefly of pancreatic juice. If this is insufficient,

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From the Gastro-Intestinal Clinic of the Jewish Hospital, Philadelphia

Read before the Physiological Society, University of Pennsylvania, Jan. 11, 1932

Presented in abstract before the Section of Medicine, College of Physicians, Philadelphia, Dec. 28, 1931

1 Heidenham, R., quoted by Boldyreff. *Quart. J. Exper. Physiol.* 8:1, 1914

2 Carlson, A. J. *The Control of Hunger in Health and Disease*, Chicago, University of Chicago Press, 1916, p. 255

3 Babkin, B. P. *Physiological Factors Determining Acidity of Gastric Juice and of Gastric Contents*. *Canad. M. A. J.* 17:36, 1927

4 Boldyreff, W. *The Self Regulation of the Acidity of the Gastric Contents and the Real Acidity of the Gastric Juice*, *Quart. J. Exper. Physiol.* 8:1, 1914

bile and intestinal juices are also secreted. He further contends that the entrance of the strong gastric acid into the duodenum, through its irritant action on the duodenal mucosa, causes antiperistalsis in the duodenum. This, in turn, drives the alkaline secretion of the intestine into the stomach until there is accumulated therein a quantity of alkaline material sufficient to lower the acidity of the gastric contents to the usual level of about 0.15 per cent hydrochloric acid.

Since Beaumont's<sup>5</sup> celebrated work on the physiology of digestion, regurgitation of intestinal contents into the stomach had been regarded more or less as a pathologic phenomenon. The work of Boldyreff, however, seemed to give a definite and an important place to such regurgitation in the normal process of gastric digestion. Boldyreff's theory has the happy faculty of appealing to the popular imagination, as it can be made to explain so readily many things concerned with gastric acidity and the pyloric mechanism. A careful survey of the literature, however, fails to reveal convincing evidence in its favor. On the other hand, it appears that definite evidence from human and, especially, from animal experimentation which tends to refute the theory has been either missed or ignored. Our most recent works on physiology still present this theory of the control of gastric acidity as an established fact.

The results of our experiments, on human beings, would indicate that the occurrence of duodenal regurgitation is not a purposeful physiologic phenomenon, but merely incidental to the resistance shown by the duodenum to the entrance of irritants, if the irritant is strong enough, its effect is reflected in the action of the pylorus. Considerable experimental literature is available regarding this theory, however, since it will be conducive to clearness to set forth the results of these investigations in connection with our own work, their consideration will be deferred until later. The results of our experiments, on human beings, fortified by those obtained by others on dogs, certainly seem to warrant a skeptical attitude regarding the efficacy of duodenal regurgitation in the control of gastric acidity.

#### EXPERIMENTAL METHOD

In 1922 Bolton and Goodhart stated that up to that time the views on duodenal regurgitation into the digesting stomach of the human subject were chiefly matters of surmise. From the evidence we were able to gather it appears that the same holds true for the present. Baird, Campbell and Hein<sup>6</sup> felt that the final solution of this problem in man

<sup>5</sup> Beaumont, W. Physiology of Digestion, ed 2, Burlington, Vt, Chauncey Goodrich, 1847.

<sup>6</sup> Baird, M. M., Campbell, J. M. H., and Hein, J. R. B. Importance of Estimating Chlorides in Fractional Test Meal Samples, and Some Experiments with Duodenal Tube, *Gov's Hosp Rep* 74:23 (Jan) 1924.

depended on finding a substance that would answer certain criteria, these were that it could be readily estimated, should not be absorbed in the stomach, should not affect the result of a test meal and should not be present normally in the secretions of the upper alimentary tract. We felt that in bromsulphalein we had such a substance. This dye, introduced and widely used for testing liver function, may be injected intravenously. From the blood stream, it is removed almost quantitatively by the liver (a very small quantity being normally taken out by the kidneys) and is excreted in the bile by means of which it reaches the second portion of the duodenum. Its ready determinability plus its other characteristics, made it an ideal substance for testing duodenal regurgitation.

In all of the experiments 5 mg per kilogram of body weight were used. For obvious reasons, each patient used in the study had first to be standardized with regard to (1) removal of the dye by the liver, (2) regularity of appearance time of the dye in the duodenum, (3) concentration of the dye in the duodenum during twenty minute periods for two hours after appearance of the dye, (4) elimination of dye by the kidneys during the test period. To accomplish this each patient received the calculated dose of dye intravenously at weekly intervals for three weeks after first intubating the duodenum with a Rehfuess tube. At each session the blood retention at the end of one-half hour was noted, appearance time of the dye in the duodenum determined, quantitative estimation of the concentration of the dye in twenty minute specimens of duodenal contents was made over a period of two hours after the appearance of the dye in the duodenum, and quantitative estimation made of the dye excreted in the urine during the test period.

It may be of interest to interpolate at this point an observation that may concern the action of bromsulphalein on the liver cells. While studying the appearance time of the dye in the duodenum, it was noted that with the evidence of the dye in the draining duodenal contents the flow from the tube became more regular and the rate of flow definitely increased. It appeared as if the dye had stimulated bile flow. This action may help to explain some of the instances of marked symptomatic relief experienced by patients at times after a bromsulphalein test is performed. One is inclined frequently to attribute such results to the psychic effect of an injection, but such results have been noted in patients in whom it has been difficult to accept this explanation for the very definite effects noted.

The duodenal appearance time in each subject varied but slightly on repeated examinations. The greatest variation in the group studied was two minutes. While the concentration of dye in the duodenum varied, it was only of importance to note that at all times during the two hour test periods there were very high concentrations of dye in the

duodenal contents The blood retentions varied within 10 per cent limits and the urinary excretion of the dye was negligible both in amount and variation The blood determination was made by the regular technic, using the usual bromsulphalein standards The same method was applied to the duodenal contents and urinary determinations, except that 1 cc of the duodenal contents, after alkalinization, was diluted to 100 cc with water, and the readings then made in the usual way This was necessary because of the very high concentrations of the dye in the duodenal contents during the two hours of the test period

After standardization, the patients were studied as follows Gastric intubation was done after a twelve hour fast The fasting stomach was completely emptied in all positions The calculated amount of dye was injected and at the duodenal appearance time of the dye, previously determined, the stomach was again completely emptied Four minutes after the appearance (allowing for the foregoing variation), the test meal was administered by mouth Within five minutes after its ingestion, the stomach was again emptied completely The amount recovered was noted, gross description made, the material withdrawn thoroughly mixed, and all but 15 cc returned by gravity through the tube to the stomach This procedure was repeated at twenty minute intervals for two hours, care being taken that the tube was kept at the same tooth-mark throughout the studies Each specimen retained was then titrated for free and total acidity and a determination of its dye content, when present, made after alkalinization with 20 per cent sodium hydroxide by the regular bromsulphalein technic At successive weekly intervals, the following test meals were used 200 cc portions of tap water at room temperature, hydrochloric acid in strengths ranging around 0.2 and 0.5 per cent, sodium bicarbonate of 1 and 5 per cent Water was first used, since it was desirable to see what response the subject would show to water, as it was to form the solvent for our other test substances In all, more than sixty determinations were so made Cases were selected to include the entire range of gastric acidity, from achylia gastrica to hyperchlorhydria Knowing the approximate concentration of dye in the duodenum, measuring the amount of gastric contents and determining the concentration of dye, when present, in this mixed specimen, enabled us to form a definite idea of the amount of regurgitation that must have taken place We do admit that duodenal regurgitation into the stomach can and doubtlessly frequently does take place, but from our experiments, we cannot ascribe any importance to this mechanism in the regulation of gastric acidity We believe that regurgitation may represent either one of two phenomena First, it may occur incidental to the process in which the duodenum attempts to reject irritants regardless of their nature (acid, alkalis, other irritants) This regurgitation, we believe is part of a reversal phenomenon of the upper

gastro-intestinal tract which has its most sensitive mechanism in the duodenum and its least sensitive in the mouth. An irritant taken into the mouth, if sufficiently strong, sets up stimuli which eventuate in expectoration. Should the irritant get past the mouth and be too irritating for the stomach, nausea and vomiting result. A still less irritating substance, not producing vomiting may be too strong for the more sensitive duodenum, and as a result duodenal regurgitation occurs. Irritants beyond this point are usually rushed onward, as we shall show in another publication.<sup>7</sup> Of considerable interest is the fact that frequently the more irritating the test meal, the less marked was the regurgitation. This will be shown elsewhere<sup>8</sup> to be due to a marked pylorospasm and anal spasm. The second phenomenon frequently responsible for regurgitation is achlorhydria. In these cases, it is due to an absence of any real pyloric control. The water meal in these instances will frequently produce more marked regurgitation than the more irritating meals which, through their very irritant action, establish some semblance of normal pyloric action and gastric emptying. This observation will also help to indicate why Iwanow<sup>9</sup> was misled in his interpretation of the frequent and marked regurgitation in achlorhydria and hypochlorhydria. He inferred that the regurgitation may be an important part of the mechanism in the production of the decreased acidity. Our experiments, on the other hand indicate that the regurgitation is evidence of a poorly controlled pyloric mechanism, and is the result rather than the cause of achlorhydria.

Similarly, our roentgenographic experiments do not warrant Cathcart's<sup>10</sup> statement that, as a general rule, the stronger the acid introduced into the fundus of the stomach, the earlier the regurgitation takes place.

The five cases cited in table 1 are merely representative of the group studied. The figures in this table certainly present several striking facts. There can be little doubt that on the introduction of a strong acid into the stomach, some adjusting mechanism that is very rapid in action sets in, further, that this mechanism certainly cannot be concerned with duodenal regurgitation. This is so, both because of the small quantitative increase in the gastric contents and, particularly, because of the practical absence of regurgitated dye, a substance which was known to be present in the duodenum in such high concentration at the time. Column A represents the approximate amount of pancreatic

7 Gershon-Cohen, J, and Shay, H. Control of the Pylorus, to be published.

8 Shay, H, and Gershon-Cohen, J. Gastric Reaction and Gastric Emptying, to be published.

9 Iwanow, W. Ueber die Regurgitation des Duodenuminhaltes in den nüchternen Magen, Arch f Verdauungsk 38 223, 1926.

10 Cathcart, E. P. Reflux from Intestine to Stomach, J. Physiol 42 433, 1911.

juice necessary to produce the difference between  $T_1$  and  $T_2$ , an amount far beyond the power of any pancreas to secrete.<sup>11</sup> As a matter of fact, if we might anticipate some of our future report,<sup>8</sup> we were able to demonstrate in our roentgenographic studies very marked pylorospasm and frequently antral spasm produced by acid similar in strength and amount to that used in these experiments, such degrees of spasm readily explain the failure of dye regurgitation above noted. *Verdünnungsst* alone could not account for the marked drop in acidity because of the slight changes in volume, nor could pyloric secretion alone be responsible for such reductions. Pyloric secretion, though known for a long time to be alkaline (Klemensiewicz),<sup>12</sup> is only faintly so, and of a low rate of secretion (Ivy,<sup>13a</sup> Takata<sup>13b</sup>). It would appear, therefore, that this rapidly adjusting mechanism may likely be one of absorption, since

TABLE 1—Five Minute Loss in Acidity of Gastric Contents with the Actual Amount (DR) of Duodenal Regurgitation and the Theoretical Amount (A) of Regurgitated Pancreatic Juice that Would Be Necessary for Such Reduction\*

Name	$T_1$	$T_2$	A (Cc)	G C	D (per Cent)	D D (per Cent)	D R (Cc)
E R	140	100	103	230	0	1,000	0
A C	150	120	77	150	20.0	4,500	1.2
M M	140	102	97	180	0	5,000	0
G H	135	80	142	260	35.0	5,000	1.8
H B	151	100	132	240	2.5	4,000	0.15

\* The test meal was given in 200 cc quantities.  $T_1$  indicates the titration of the test meal in terms of tenth normal hydrochloric acid,  $T_2$ , the titration of free hydrochloric acid (tenth normal) in the total gastric contents, removed within five minutes after ingestion of the test meal, A, the approximate amount of 0.65 per cent sodium carbonate necessary to produce the reduction from  $T_1$  to  $T_2$ , G C, the amount of gastric contents removed from the stomach within five minutes after the ingestion of 200 cc of the test meal, D, the percentage of dye in gastric contents in G C, D D, the percentage of dye in duodenal contents at same time as D, this reading having been previously determined, D R, the amount of regurgitation of D D necessary to produce concentration of dye found in D.

Note—Regular bromsulphalein standards were used to determine concentration of dye.

this could account both for the rapid drop in acidity and the slight changes in volume.

We were entirely unable to correlate the amount of duodenal regurgitation as measured by the concentration of dye in the gastric contents with the degree or change of gastric acidity. As a matter of fact, the greatest amount of dye regurgitated during all the experiments yielded a reading of 360 per cent, and occurred during the course of a plain water meal in a case of true achylia gastrica (table 2). Furthermore, so far as the Boldreft theory is concerned, it is paradoxical that the

11 Ivy, A. C. Personal communication.

12 Klemensiewicz, R. Ueber den Succus pyloricus, Sitzungsberichte der Akademie der Wissenschaften, Wien **71** 221, 1875.

13 (a) Ivy, A. C. Studies on the Secretion of the Pyloric End of the Stomach, *Am. J. Physiol.* **49** 142, 1919, (b) Takata, M. Studies in the Gastric Juice. IV. On the Pyloric Juice, *J. Biochem.* **2** 33, 1923.

bicarbonate test meals often showed greater evidence of regurgitation than did the acid meals (table 3). These phenomena are readily explained if the rôle of the pyloric sphincter is kept in mind as previously indicated. In addition, it is to be noted that the acid meals around 0.2 per cent were apt to produce more marked evidence of regurgitation than the meals ranging around 0.5 per cent (table 2). This also is to be expected in the light of our roentgenographic experi-

TABLE 2—*Comparison of Duodenal Regurgitation Resulting in the Same Patient from a Water, a Strong Acid and a Weak Acid Meal Respectively\**

Time, Min	200 Cc H <sub>2</sub> O				200 Cc 0.547% HCl				200 Cc 0.2% HCl			
	FA	TA	G C (Cc)	Dye, per Cent	FA	TA	G C (Cc)	Dye, per Cent	FA	TA	G C (Cc)	Dye, per Cent
FR	0	10			0	10			0	5		
5	0	5	162	90	120	130	150	20	15	50	195	20
20	0	5	12	60	100	105	95	30	30	35	65	60
40	0	5	15	20	70	75	45	40	5	15	15	60
60	0	5	20	40	55	60	30	30	0	10	4	100
80	0	5	18	55	35	45	5	30	0	10	8	180
100	0	10	20	960	10	20	5	20	0	5	7	50
120	0	5	15	150	Empty				0	5	5	100

\* FA indicates free hydrochloric acid, TA, total acidity, G C, amount gastric contents, FR, fasting residuum. The data illustrate the much higher degree of regurgitation with the water meal in a case of achylia gastrica. Also note the greater degree of regurgitation with the weaker acid meal as compared to the stronger acid.

TABLE 3—*Comparison of Duodenal Regurgitation Resulting in the Same Patient from a Relatively Strong Acid and a Relatively Strong Alkali Meal\**

Time, Min	200 Cc 0.511% HCl				200 Cc 7% NaHCO <sub>3</sub>			
	FA	TA	G C (Cc)	Dye, per Cent	FA	TA	G C (Cc)	Dye, per Cent
FR	0	10			0	5		
5	100	107	230	0	0	10	185	40
20	72	65	195	30	1	1	75	110
40	30	15	80	15	1	1	20	95
60	5	17	10	10	1	1	14	100
80	5	18	20	5	0	5	22	60
100	0	10	15	25	0	5	13	40
120	0	10	10	0	0	2	15	40

\* FR indicates fasting, residuum, A, alkaline in the reaction.

ments.<sup>8</sup> The reason, of course, is that the 0.2 per cent strength, ranging a little above the concentration of duodenal toleration (0.15 per cent) is not strong enough to produce marked pylorospasm, but sufficiently irritative to be rejected by the duodenum and so carry back with it duodenal contents.

Certain additional facts which may be worthy of note have presented themselves during the course of these experiments. The first of these concerns the theory of a dissociated regurgitation of bile and pancreatic juice from the duodenum into the stomach—an idea which appears from the literature to be generally accepted, but which has no basis in fact. Any number of papers may be quoted in which this is



accepted on the finding of trypsin in the gastric contents in the absence of visible bile pigment. While anatomic evidence (Baldwin,<sup>14a</sup> Behrend<sup>14b</sup>) shows that an accessory pancreatic duct opens into the duodenum from  $\frac{3}{4}$  to 1 inch higher than the common bile duct, recent physiologic evidence<sup>15</sup> shows that the flow of bile and pancreatic juice into the duodenum is coincident. We have further demonstrated the fallacy of dissociated regurgitation by showing in our experiments that bile pigment in low concentration in gastric juice is not readily recognizable to the naked eye. Bromsulphalein and bile were added separately to portions of gastric juice previously shown to be free of either of these substances. The one containing the dye was made alkaline. Both were then diluted separately until in the one the dye was just recognizable and in the other the bile tinge was just perceptible. The

TABLE 4—*Relatively Rapid Loss of Acidity in the Gastric Contents in the First Five Minutes as Compared to the Total Lost in an Hour, After the Ingestion of Acid Meals*\*

Case	Per Cent Acid Test Meal	Per Cent Acid Lost in		Acid in Ewald Meal
		5 Min	60 Min	
1	0.547	20	65	0
	0.200	18	100	
2	0.547	19	76	+
	0.244	7	45	
3	0.490	40	94	—
	0.200	18	82	
4	0.510	27	93	N
	0.220	5	83	

\* N indicates normal acid response, +, hyper response, —, hypo response, and 0, achylorhydria.

dye concentration was then determined by the usual procedure, while the concentration of bile was determined by the van den Bergh technic. Repeated estimations and calculations of the relative concentrations of the two pigments showed that, on the average, there was required at least five times the concentration of bile as compared to alkalinized bromsulphalein to permit detection by the naked eye with certainty. It seems highly probable, therefore, that previous investigators, believing they had found regurgitated pancreatic juice in the absence of regurgitated bile, were simply erring by using a chemical test for one substance and a visual test for the other, at the same time ascribing

14 (a) Baldwin W. M. Pancreatic Ducts in Man, Together with a Study of the Microscopical Structure of the Minor Duodenal Papilla, *Anat. Rec.* 5:197, 1911. (b) Behrend M. Surgical Diseases of the Gall Bladder, Liver and Pancreas and Their Treatment, Philadelphia, F. A. Davis Company, 1927, p. 50.

15 McClure, C. W., and Wetmore, A. S. Studies in Pancreatic Function. Enzyme Concentration of Duodenal Contents After the Ingestion of Pure Foodstuffs and Food Mixtures by Normal Men. *Boston M. & S. J.* 187:882, 1922.

equal degrees of sensitivity to both Dodds and Robertson,<sup>16</sup> recently studying lactic acid in the gastric contents, experienced difficulties which they were able to show were due to occult bile regurgitation

Another factor which assumed prominence in our work was the rate at which the gastric acidity was lowered Migai<sup>17</sup> found that a 0.5 per cent solution in the stomach lost 75 per cent of its acidity after an hour, while a 0.3 per cent solution lost 44 per cent, and a 0.1 per cent solution lost about 8 per cent in the same time Boldyreff<sup>6</sup> cited these experiments as part of the evidence on which he has built up his theory Migai, however, failed to observe that the percentage of neutralization which occurs in the first five minutes after the introduction of the acid is far out of proportion to the neutralization which takes place in the remainder of the hour, this first five minute neutralization being inexplicable on the basis of Boldyreff's theory Table 4 illustrates the disproportion in the amount of acid loss during the first five minutes

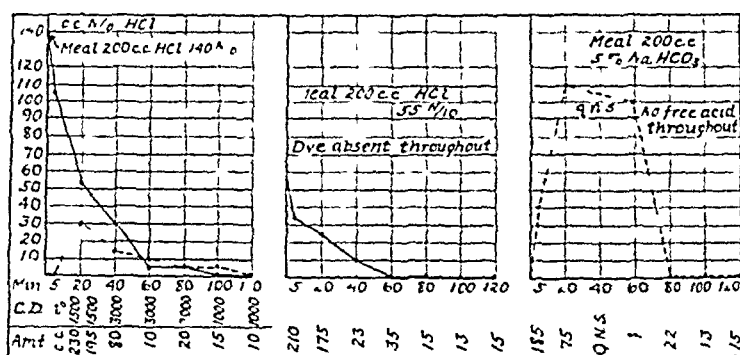


Chart 1—Graphic picture of the free acidity curve and percentage of dye during the course of the various test meals given to the same patient on successive days under experimental conditions described in the text. In this and in chart 2, *CD* indicates the previous determination of the concentration of dye in the duodenum at corresponding times, *Amt*, the gastric volume at corresponding times, the solid line, free hydrochloric acid, and the broken line, the percentage of dye in the gastric contents

as compared to the total loss during the first hour after ingestion of the acid meal

Charts 1 and 2 will deserve a moment's consideration. Chart 1 represents a graphic picture of the free acidity curve and percentage of dye during the course of test meals of 200 cc each of 140 tenth-normal hydrochloric acid (0.511 per cent), 55 tenth-normal hydrochloric acid (0.20 per cent) and 5 per cent sodium bicarbonate solution, given to the same patient on successive days under the experimental conditions

16 Dodds, E. C., and Robertson, J. D. Origin and Occurrence of Lactic Acid in Human Gastric Contents, *Quart J Med* **23**:175, 1930

17 Migai. Diss., St Petersburg, 1909, quoted by Bayliss, W. M. Principles of General Physiology, ed. 4, London, Longmans, Green & Co., 1924, p. 371

described. The concentrations of dye in the duodenum (C D) at corresponding times are noted as well as the total amounts of gastric contents (Amt) recovered from the stomach at corresponding periods. It will take little mathematics to see what ridiculously small amounts of regurgitation the dotted lines represent, but it will be of interest to note what a greater proportion of regurgitation occurred with the sodium bicarbonate meal, even though no free acid was present throughout as a matter of fact the notes on this case show that the gastric contents recovered were for the most part alkaline in reaction.

Were one to examine the graph alone without considering how much actual regurgitation the broken curve really represents, one could

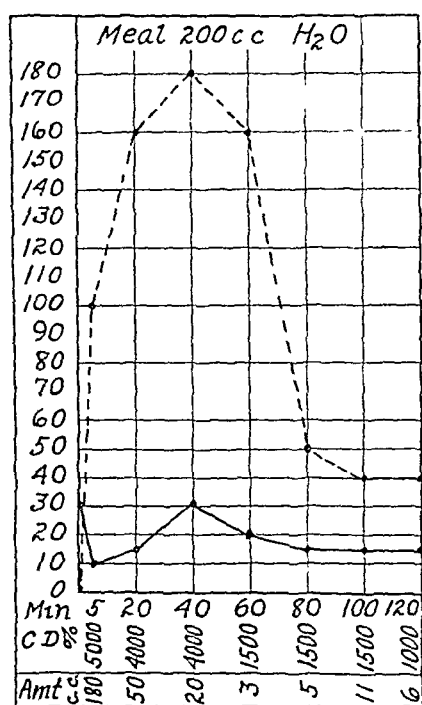


Chart 2—Graphic representation may be misleading, if the degree of regurgitation is not considered in relation to the concentration of the test substance in the duodenum to the total gastric contents and to the total test substance present therein at a given time. The apparently high concentration of dye (180 per cent) in the stomach contents at the end of forty minutes fades into insignificance if considered in relation to the foregoing factors.

readily say that a definite increase in regurgitation was noted. Chart 2 makes this point even more obvious. This chart, showing such an apparently large amount of regurgitation, also shows the peak of the regurgitation to correspond with the peak of the acid curve, but when one calculates the actual amount of regurgitation, one sees that less than 2 cc of duodenal contents would be sufficient to have produced the concentration of dye noted in the stomach.

A brief consideration of the important experimental data that have preceded our studies will now be of interest and then analysis, we think, will help to fortify our contention that duodenal regurgitation in man as well as in dogs is probably a negligible factor in the control of gastric acidity.

*Experiments in Which Pancreatic or Duodenal Regurgitation is Prevented*—From his own experiments, Boldyreff<sup>1</sup> stated that the exclusion of the pancreatic juice alone was practically as efficacious in preventing the normal loss of gastric acidity as total exclusion of all juices. This conclusion, based on pancreatic duct ligation in dogs,<sup>18</sup> is not supported by similar experiments of more recent date. Yesko<sup>19</sup> found that the ligation of the pancreatic ducts in dogs caused no striking changes in gastric acidity. Seven dogs similarly treated by Fauley and Ivy<sup>20</sup> showed the average gastric acidity following the operation to be increased in three, a negligible difference in three and actually decreased in one, as compared to that before the operation. Further convincing contrary evidence may be had in the experiments of McCann,<sup>21</sup> who studied the mechanism of gastric acid control in dogs before and after the Mann-Williamson operation. This operation short-circuits all the duodenal contents into the lower portion of the ileum, while the gastric contents pour directly into the upper portion of the jejunum. This procedure makes regurgitation of duodenal contents into the stomach impossible. Postoperative fractional analyses on these animals show no variations from the curves found before the operation so far as they represented the chemistry of digestion or the control of the acidity of the juice. The same adequate control of the gastric acidity occurred after operation as before. He further showed that with the addition of fat (olive oil) to the test meals, the free acid was not controlled any better in the normal dog than in the dog operated on, even though fat may augment the factor of regurgitation in the normal dog. His results suggest that the control of gastric acidity depends essentially on some intragastric mechanism.

McCann<sup>22</sup> further demonstrated how little effect duodenal contents had on gastric acidity by reversing the foregoing experiments, that is, he drained the whole volume of duodenal contents into the fundus of the stomach. Animals so operated on showed the usual characteristic

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18 Boldyreff, W. Einige neuen Seiten der Tätigkeit der Pankreas, *Ergebn d. Physiol* **11** 121, 1911.

19 Yesko, S. A. The Effects of Ligation of the Pancreatic Ducts on Gastric Secretion, *Am J Physiol* **86** 483, 1928.

20 Fauley, G. B., and Ivy, A. C. Effect of Exclusion of Pancreatic Juice on Gastric Digestion, *Am J Physiol* **89** 428, 1929.

21 McCann, J. C. Studies on the Control of Acidity of the Gastric Juice, *Am J Physiol* **89** 483, 1929.

22 McCann, J. C. Experimental Ulcer, *Arch Surg* **19** 600 (Oct.) 1929.

curves of normal digestion with average normal values for free acid at the end of the period. The same preliminary rise in the value of total acid and neutral chlorides was followed by the usual type of curve for free acid. There was the terminal rise in neutral chlorine in both instances, before and after operation. McCann's work leaves little room for doubt that in dogs, at least, the gastric acid control is independent of anything that may be added from the duodenum.

The closest approach to the same type of experiment in human beings was the work of Baird, Campbell and Hein<sup>6</sup>. These experimenters used the method of double intubation, one tube being in the duodenum, the other in the stomach. Continuous suction was exerted on the duodenal tube, the specimens being segregated into fifteen minute portions, while fifteen minute extractions were made through the gastric tube. Each gastric and duodenal specimen was estimated for free and total acidity and total chlorides. Duplicate experiments were carried out on the same patient, test meals of water, sodium bicarbonate and hydrochloric acid were used. These investigators reasoned that if continuous suction were exerted on the duodenal tube, so that everything entering the duodenum was at once sucked out, regurgitation would be prevented. Thus, in the absence of regurgitation and the failure of neutralization they expected the curves for chlorides and for total acid to be the same. However, they actually found that for the stomach the curves for chloride and for acid remained as widely separated as when the test meals were given and no duodenal suction was applied.

*Evidence Based on the Presence of Pancreatic Enzymes in the Gastric Contents*—Numerous experiments have been described presenting the presence of one or the other of the pancreatic enzymes in the gastric contents as irrefutable evidence of duodenal regurgitation. While no doubt true, the interpretation of these findings in relation to the control of gastric acidity is far from convincing to us from our analysis of these reports. Such evidence presented has found its chief support in the work of Spencer, Meyer, Rehfuess and Hawk<sup>23</sup>. They argued that if duodenal regurgitation does occur, one should be able to recognize some of the constituents of the duodenal secretions in the material removed from the stomach. They selected trypsin as the best available test substance, using a method modified by Spencer for its determination. While they do show variations in the amount of trypsin present in the stomach at different times during the digestive phase, their charts fail to demonstrate the extent of regurgitation. At no place do they tell us what the normal pancreatic or duodenal contents show by Spencer's method for trypsin determination. It therefore does

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<sup>23</sup> Spencer, W. H., Meyer, G. P., Rehfuess, M. E., and Hawk, P. B. Direct Evidence of Duodenal Regurgitation and Its Influences upon the Chemistry and Function of the Normal Human Stomach, *Am J Physiol* **39** 459, 1915.

not appear likely that the fluctuation in their gastric determinations can be interpreted as a measure of duodenal regurgitation. Their experiments indicate that duodenal regurgitation does take place, but do not necessarily prove that it is an important mechanism in the control of gastric acidity. The trypsin determinations of Medes and Wright<sup>24</sup> are subject to the same criticism. Ehrenreich,<sup>25</sup> from similar studies, was unable to reach any conclusion, because he found trypsin to be present in only thirty-seven of sixty-one instances in the gastric contents. He concluded that the question of duodenal regurgitation is not so simple as Boldyreff suggests. MacLean and Griffiths<sup>26</sup> were unable to show any relationship between the variations in tryptic activity of the gastric contents and the curves of gastric acidity. Ehrmann and Lederer<sup>27</sup> found that trypsin, while usually present in an Ewald meal aspirated after forty-five minutes, was usually low and in no case increased if acid was given with the meal. Their findings are not surprising in the light of experiments showing the effect of irritants on the pyloric mechanism to be detailed in a subsequent publication.

Robitschek<sup>28</sup> reported as confirmatory evidence for the Boldyreff theory the case of a patient who fifteen years previously had swallowed lye, resulting in a complete stricture of the esophagus. A gastrostomy, with the esophagus sutured into the skin, assured no connection between the mouth and the stomach. As evidence of duodenal regurgitation into the stomach, the presence of a diastatic ferment was offered. This was determined by the Wohlgemuth method,<sup>29</sup> which yielded a reading of 3 for the fasting stomach contents and of 42 after a test meal. However, on the same basis, Wohlgemuth reported diastatic figures for pancreatic juice as ranging from 12,000 to 40,000. One can readily see how little actual regurgitation of pancreatic juice the figures of Robitschek represent. Gross<sup>30</sup> reports a similar case, but fails to give any figures for his diastatic values.

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24 Medes, I. G., and Wright, C. W. Studies on Duodenal Regurgitation, *J Clin Investigation* **6** 403, 1928.

25 Ehrenreich, M. Ueber die kontinuierliche Untersuchung des Verdauungsablauf mittels der Magenverweilsonde, *Ztschr f klin Med* **75** 231, 1912.

26 MacLean, H., and Griffiths, W. J. The Factors Influencing the Concentration of Hydrochloric Acid During Gastric Digestion, *J Physiol* **65** 63, 1928.

27 Ehrmann, R., and Lederer, R. Ueber die Wirkung der Salzsäure auf die Fermentsekretion des Magens und der Bauchspeicheldrüse, *Klin Wchnschr* **45** 1450, 1909.

28 Robitschek, W. Ueber physiologische Regurgitation von Pankreassaft in den Magen, *Wien klin Wchnschr* **35** 604, 1922.

29 Wohlgemuth, J. Untersuchungen über die Diastasen, *Biochem Ztschr* **9** 10, 1908.

30 Gross, O. Ueber den physiologischen Rückfluss von Pankreassaft in den Magen, *Arch f klin Med* **132** 121, 1920.

*A Mathematical Consideration of Duodenal Regurgitation, Reaction in the Duodenum*—It is difficult to understand how regurgitation from such an area as the duodenum which has recently been shown to be more often acid than alkaline in reaction,<sup>31</sup> can materially influence the acidity of the stomach. Martin<sup>32</sup> from his studies of duodenal reaction, concludes that the normal duodenal contents are nearly neutral but under any digestive procedure, are likely to become acid. Our own experiments, to be detailed later, in which the duodenal contents containing large quantities of bromsulphalein were collected, showed these contents to be, in most cases, neutral or acid, since the dye was not discernible until the material was alkalinized. Such was also the case in three instances of true achylia gastrica (histamine). The duodenal contents collected from these patients, containing large quantities of bromsulphalein which had been previously injected intravenously, failed to give any evidence of its presence until alkali was added. This is particularly significant when we consider that no acid could have been added from the stomach in these patients. This fact becomes still more striking if we recall that bromsulphalein ceases to be colorless at a  $pH$  of 7.2.

Setting aside, for the moment, this evidence, let us see what amounts of regurgitation would be necessary to satisfy the experiments presented in support of the Boldyreff theory. The majority of these experiments involved the introduction of 0.5 per cent hydrochloric acid into the stomach in amounts ranging between 100 and 200 cc. We used 200 cc quantities in our experiments. Assuming that Boldyreff's contention that 0.15 per cent hydrochloric acid is the upper limit of concentration at which hydrochloric acid is acceptable to the duodenum, granting that the pancreatic juice is the most alkaline secretion reaching the duodenum, admitting the alkalinity of pancreatic juice to be 0.65 per cent sodium carbonate as quoted by Boldyreff<sup>4</sup> (though this is stronger than recently found by Ivy<sup>11</sup>), it would still take approximately 120 cc of *undiluted* pancreatic juice to reduce 200 cc of 0.5 per cent hydrochloric acid to 0.15 per cent allowance already being made for the dilution reduction in the stomach. This amount would have to be delivered to the stomach in a comparatively short time, about one hour, to produce the desired result. Ivy<sup>11</sup> has shown that the greatest degree of secretory stimulation possible in a dog's pancreas is about 70 cc per hour, an amount far short of that required in the animal experiments, and certainly in our human experiments if considered on

31 Mann, F. C., and Bollman, J. L. The Reaction of the Content of the Gastro-Intestinal Tract, *J. A. M. A.* **95** 1722 (Dec 6) 1930.

32 Martin, L. The Hydrogen Ion Concentration of Successive Portions of Duodenal Contents Following Stimulation with Magnesium Sulphate, *Arch. Int. Med.* **39** 275 (Feb) 1927.

a proportionate basis. The diluting effect of the other intestinal juices is also disregarded in the foregoing calculations. The Boldyreff theory would also assume considerable addition of fluid to the gastric contents before emptying occurred. Such is not borne out in our table 1 showing the rapid drop in acidity in a five minute period, with comparatively small changes in volume of the gastric contents.

*Experimental Evidence Based on the Curves for Gastric Chlorides*—Bolton and Goodhart<sup>33</sup> estimated the total chlorides as a measure of gastric secretion and the inorganic chlorides as a measure of the amount of duodenal regurgitation. They showed that the curve of inorganic chlorides gradually rises from the beginning of digestion, with that of the active hydrochloric acid to more or less the same level. This rise they attribute to the neutralization of some of the hydrochloric acid secreted by what alkali happens to be present in the food, swallowed in the saliva or contained in the gastric mucus or pyloric juice, as well as to the decomposition of organic salts in the food by the hydrochloric acid. At the point at which the curve of active hydrochloric acid falls, the curve of inorganic chlorides continues to rise sharply, following that of the total chlorides at a somewhat lower level. This second rise they attribute to neutralization of the hydrochloric acid by the regurgitated duodenal juice.

While one does not deny the aforementioned series of changes in their relation to each other subsequent experimental evidence indicates that the foregoing explanation of the phenomena is certainly at fault. Thus, MacLean and Griffiths,<sup>34</sup> who studied the curve of gastric chlorides as well as trypsin in the gastric contents, were unable to demonstrate a rise in trypsin content parallel with the marked rise in neutral chlorides and subsequent fall of acidity. Of still greater significance is the demonstration of the foregoing relative changes of neutral chlorides and free acid in the secretions of a Pavlov pouch in dogs into which no duodenal regurgitation could occur. This was shown by MacLean, Griffiths and Williams<sup>34</sup>. Finally, incontrovertible evidence in this respect is again available in the work of McCann,<sup>22</sup> who found the same terminal rise in neutral chlorine and drop in hydrochloric acid both before and after his short-circuiting operations.

#### CONCLUSIONS

Granting that regurgitation from the duodenum into the stomach frequently occurs, we differ strongly from Boldyreff in the interpreta-

33 Bolton, C, and Goodhart, G W. Duodenal Regurgitation into the Stomach During Gastric Digestion, *Lancet* 1:420 (March 4) 1922.

34 MacLean, H, Griffiths, W J, and Williams, B W. Variations in the Acidity and Total Chloride Contained in the Secretion from an Isolated Pavlov Pouch in the Dog, *J. Physiol.* 65:77, 1928.



tion and significance of this regurgitation basing our contention on the following evidence

1 The introduction of weaker acids (0.2 per cent hydrochloric acid) into the stomach frequently produces greater amounts of regurgitation than do stronger acids (0.5 per cent)

2 Ingestion of alkalis (1.0 and 5.0 per cent sodium bicarbonate) often produces more marked regurgitation than either of the aforementioned acids, even though the gastric contents remain alkaline or anacid throughout the test period

3 The greatest amount of regurgitation noted during all of our experiments occurred in a case of true achylia gastrica during the course of a plain water meal

4 The reaction of the duodenal contents is such that even if considerable regurgitation did take place, it could not be efficacious in lowering gastric acidity

5 The duodenal contents are not sufficiently alkaline to change the color of bromsulphalein, a dye which changes color at a  $p_H$  of 7.2, this even in cases of true achylia gastrica

6 The amount of pancreatic juice necessary to produce the reductions in gastric acidity noted is far beyond the ability of any pancreas to secrete during the time allotted

7 Dissociated regurgitation of pancreatic juice and of bile is based on a fallacy in experimentation

8 With the introduction of acids into the stomach, some very rapid mechanism is brought into play. This mechanism being neither one of neutralization nor of dilution, we believe is very likely one of absorption

Therefore, as a result, we have been unable to ascribe any significance to duodenal regurgitation in relation to gastric acid control. We are in agreement with McCann, whose results suggest that this control depends essentially on some intragastric mechanism. From the experiments cited in this paper and from roentgenographic evidence to be detailed elsewhere, we are inclined to look on duodenal regurgitation as part of the pyloric mechanism

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# INTRINSIC GASTRODUODENAL LESIONS AS CAUSATIVE FACTORS OF HEMATEMESIS

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Previous study<sup>1</sup> has revealed that intrinsic gastroduodenal lesions are responsible for approximately 90 per cent of all cases of hematemesis. Since hematemesis is usually produced by such lesions, it is justifiable to consider their diagnostic significance in detail, for an accurate diagnosis is highly desirable and is the key to eventual successful treatment. The outstanding factor of value in the differential diagnosis of such intrinsic lesions is the correlated consideration of (1) an accurately recorded and perused history and (2) laboratory studies, chiefly roentgenologic observations. Among intrinsic gastroduodenal lesions producing hematemesis, the most common are peptic ulcer and gastric carcinoma, while nonspecific inflammatory lesions, mucosal erosions, benign tumors, gastric syphilis and tuberculosis make up a small proportion of hemorrhagic lesions. This enumeration of some of the intrinsic gastroduodenal diseases producing hematemesis reveals that they are of almost equal medical and surgical significance, and, consequently, cooperative treatment is essential. It has been pointed out that it is usually not essential that an accurate diagnosis be made before treatment is begun, since relatively simple medical measures will usually be sufficient to control the bleeding producing hematemesis. The precipitation of hasty surgical treatment is frequently ineffective in controlling this bleeding and may jeopardize rather than increase the patient's chances.

Balfour,<sup>2</sup> Miller,<sup>3</sup> Bastedo<sup>4</sup> and others have pointed out the great frequency of intrinsic gastroduodenal lesions as the causes of hema-

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1 Rivers, A. B., and Wilbur, D. L. The Diagnostic Significance of Hematemesis, *J. A. M. A.* **98** 1629 (May 7) 1932

2 Balfour, D. C. Hematemesis, *Tr. Coll. Phys.* **44** 236, 1922

3 Miller, T. G. Gastric Hemorrhage from the Internist's Point of View, *Pennsylvania M. J.* **32** 237 (Jan.) 1929

4 Bastedo, W. A. Medical Measures Used in the Treatment of Hematemesis, *Tr. Am. Gastro-Enterol. A.* **30** 107, 1927, *M. J. & Rec.* **126** 333 (Sept. 21) 1927

temesis It seems almost universally accepted that peptic ulcer is the chief cause of vomiting of blood, and yet, as recently as 1930, Hughes<sup>5</sup> attempted to discredit this belief and stated that, in twenty-five years of experience, he had observed only two cases of true hemorrhage as a result of peptic ulceration The earlier studies of White<sup>6</sup> concerning gastrostaxis seem worthy of reevaluation in the light of recent observations and the present benefits of more accurate studies now possible Consideration of the incidence, mechanism and diagnosis of the various causes of hematemesis will be included

#### MATERIAL FOR STUDY

The present study includes the data obtained from a review of the histories of all patients who came to the Mayo Clinic complaining of vomiting of blood during the years 1927 and 1928 Those giving a history solely of melena were not included Since the tabulation of the data in cases studied in 1928 represents an almost exact reduplication of those tabulated for 1927, there is assurance that the estimations presented are reasonably accurate Our material includes 668 cases, in 236 of which diagnosis was made after careful clinical investigation, without surgical exploration, and in the remaining 432 cases, we have the additional information obtained through careful surgical exploration In 602 (91 per cent) of these 668 cases, hematemesis was due to intrinsic gastroduodenal lesions Except that relatively few cases in which acute infectious diseases are accompanied by hematemesis reach us for diagnosis, and that perhaps a larger proportion of surgically treated peptic lesions are represented, the data obtained should not be at great variance with those observed in the general practice of medicine

#### RESULTS

A summary of the results of the study undertaken in 602 cases of intrinsic gastroduodenal lesions as causative factors of hematemesis is presented in table 1, their relative significance is tabulated graphically in table 2 Cases in which exploration was done and those in which it was not done are reviewed in table 3 There is no great difference in the types of cases represented among the groups in which exploration was done and those in which it was not done, although, as would be expected in the latter group in some instances the diagnosis could not

<sup>5</sup> Hughes, Basil Hematemesis as a Symptom of Gastric or Duodenal Ulcer, *Lancet* **2** 1346 (Dec 20) 1930

<sup>6</sup> White, W Hale An Address on Gastrostaxis, or Oozing of Blood from the Mucous Membrane of the Stomach, *Lancet* **2** 1189 (Nov 3) 1906, Some Forms of Haemorrhage Which Are Difficult of Explanation, *ibid* **1** 416 (Feb 17) 1912

be as positively established as in those in which surgical intervention was performed. This is particularly true of the group classified as having a history of ulcer, but roentgenologically negative. A positive diagnosis of ulcer was not made in these cases in the absence of roentgenologic confirmation. Undoubtedly, exploration would have placed

TABLE 1—*Incidence of Lesions*

Lesion	Number	Per Cent
Duodenal ulcer	356	59.20
Gastric ulcer	43	7.10
History of gastric ulcer, but roentgenologically negative	22	3.60
Secondary ulcer	92	15.30
Carcinoma of stomach	84	13.80
Adenoma of duodenum	1	0.16
Myoma of stomach	1	0.16
Gastric syphilis	1	0.16
Cholecystoduodenal fistula	2	0.32

TABLE 2—*Relative Frequency of Intrinsic Gastroduodenal Lesions as Compared to Other Causes of Hematemesis*

Lesion	Number	Per Cent
Ulcer	513	76.80
Carcinoma	84	12.60
Other benign lesions	5	0.83
Other causes	67	9.65

TABLE 3—*Incidence of Lesions in Explored and Unexplored Cases*

Explored	Number	Per Cent
Duodenal ulcer	245	56.6
Gastric ulcer	33	7.7
Secondary or reactivated ulcer	53	12.7
Carcinoma of stomach	56	13.0
Adenoma of stomach	1	0.2
Myoma of stomach	1	0.2
Gastric syphilis (with hepatic involvement)	1	0.2
Cholecystoduodenal fistula	2	0.4
Unexplored		
Duodenal ulcer	111	47.0
Gastric ulcer	10	4.2
History of ulcer, but roentgenologically negative	22	9.3
Secondary or reactivated ulcer	39	16.5
Carcinoma of stomach	28	11.9

some of the cases in the ulcer group. The pathologic processes that may be responsible for bleeding in some cases of apparent peptic ulcer are such that it is not surprising that the lesion at times is not demonstrable roentgenologically, although at the time the present study was made (from 1927 to 1928) the diagnosis of peptic ulcer by this method had reached a high degree of accuracy. The presence of localized or diffuse areas of inflammatory reaction, of nonspecific character, in the stomach or duodenum or surrounding a gastro-enteric stoma, may lead not only to symptoms suggestive of peptic ulceration but also to hemoi-

hage, as demonstrated by one of us (D<sup>1</sup> Rivers<sup>7</sup>), and yet such areas may not produce sufficient abnormality in the contours or functions of these organs to be recognizable roentgenologically. In addition, the failure of the roentgenologist or the surgeon to find evidence of ulceration in the stomach or duodenum at the time of examination may be due to the fact that such examination is carried out several weeks after the occurrence of the bleeding. During this interval it is conceivable that many small lesions will heal completely.

#### PEPTIC ULCER

It is apparent that peptic ulcer is the greatest offender in the causation of hematemesis, since more than 75 per cent of the total number of cases in which this symptom occurred presented evidence of duodenal benign gastric or anastomotic ulceration. Similarly, peptic ulcers were responsible factors in more than 85 per cent of the cases of hematemesis due to intrinsic gastroduodenal lesions.

It is generally considered that approximately 20 per cent of all duodenal ulcers bleed. The clinical varieties and exciting causes of bleeding are many, the bleeding may be occult or gross, large or small in amount, and may occur as melena or hematemesis, or both. Primary hemorrhage is rarely fatal. It has been stated by others that hematemesis in the presence of a peptic ulcer is usually an indication of the presence of gastric ulcer, and that duodenal ulcers rarely provoke vomiting of blood. On the contrary, if they bleed, melena is the expected result. Our experience does not bear out this statement. Matthews<sup>8</sup> expressed the belief that the bleeding of a duodenal ulcer is more serious than that of gastric ulcer, because the bleeding is more severe and more continuous.

Ulcers on the anterior wall of the duodenum bleed less frequently than ulcers of the posterior wall because of the less abundant supply of blood to the anterior wall, which is relatively anemic. The posterior wall of the duodenum is more vascular, and ulcers in this area more readily penetrate into the pancreas, which is quite vascular. In the present series, duodenal ulcers accounted for 356 of the 602 cases (59 per cent) of hematemesis due to intrinsic gastroduodenal lesions. In an additional 22 cases, the history was positive for ulcer, but the roentgenologic examination was not confirmative.

The mechanism in the production of the bleeding may depend on a distant cause in addition to the local lesion of the duodenum. Although

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<sup>7</sup> Rivers, A. B. A Clinical Study of Duodenitis, Gastritis and Gastrojejunitis, *Ann Int Med* 4:1265 (April) 1931.

<sup>8</sup> Matthews, Edwin. The Clinical Significance of Hematemesis in Gastro-Intestinal Diseases, New York, Oxford University Press, 1928, p. 120.

the essential underlying cause of the bleeding is rupture of a blood vessel, the type of vessel ruptured and the agent provoking the rupture may vary considerably. Three types of vessels may produce such bleeding. 1 A moderate-sized or a large vessel may be penetrated as a direct result of the process of peptic ulceration, such vessels are frequently sclerotic and lie at the base of the ulcer, which generally is in the posterior wall of the duodenum, or which has perforated through into the pancreas. Rarely, a large vessel, such as the pancreaticoduodenal and the splenic or a large gastric vessel may be ruptured, and under such circumstances the bleeding may rapidly become of serious significance. Bleeding from this type of vessel is usually extensive and frequently produces hematemesis of bright red blood in large amounts, followed by melena. 2 This type is comprised of the group of small, actively and passively congested vessels which surround an acutely or subacutely inflamed area, and which are easily ruptured by trauma, by excessive venous stasis or by changes in the blood itself. Bleeding under such circumstances is usually slow and oozing, but the loss may be considerable. Although hematemesis is less common as a result of this type of lesion, it nevertheless occurs, melena is the more common result. 3 Vessels in the buds of vascular granulation tissue in the base of the ulcer, formed during the process of healing, may bleed profusely when the buds break off. Associated disease in other organs which produces venous stasis of the stomach or duodenum may produce conditions favorable for bleeding from a peptic ulcer, which, in the absence of such stasis, would not necessarily bleed.

Among the more common exciting factors productive of bleeding from gastroduodenal lesions may be mentioned excessive physical exertion, acute infection, alcohol, fatigue or emotional strain and hypersensitive types of reaction. It is well known that physical strain, particularly heavy lifting, will provoke bleeding from an ulcer, which is presumably due to the associated elevation of both arterial and venous pressure, with rupture of a vessel within the ulcer. Acute infections or exacerbations of chronic infections, particularly of the mouth and upper part of the respiratory tract, may be productive of gastrointestinal bleeding, probably as a result of associated lighting up of the inflammatory process surrounding the ulcer. Such changes leading to the bleeding have been demonstrated clinically by bouts of bleeding from ulcer following extraction of teeth or tonsils, and experimentally by the work of Rosenow.<sup>9</sup> Alcohol, by its direct irritation of the ulcer or by stimulation of excessive gastric secretion, provokes bleeding. Fatigue and emotional strain frequently provoke sufficient flare-up

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<sup>9</sup> Rosenow, E. C. The Causation of Gastric and Duodenal Ulcer by Streptococci, *J. Infect. Dis.* **16** 333 (Sept.) 1919

of the ulcer to result either in further penetration, which may include a blood vessel, or else exacerbation of the inflammatory reaction surrounding the ulcer. Burns and hypersensitive types of reaction are among the rare causes of bleeding from an ulcer. It is well known that extensive burns may lead to acute ulcers of the duodenum, the so-called Curling's ulcer, which may bleed, or bleeding may occur without any actual ulceration and may be so extensive as to be a factor in producing a fatal result. This recently occurred in a case under our observation. It is to be pointed out that peptic ulcer may be present coincidentally with many other diseases for example, cirrhosis of the liver, coronary thrombosis, diabetes, tabes with gastric crisis, and so forth, which have been reported as leading to gastric hemorrhage, and it may be that the associated ulcer is the actual cause of such bleeding.

Occasionally, a bleeding ulcer on the posterior wall of the duodenum will not produce sufficient change to be demonstrable by inspection of the duodenum at operation. Incision of the anterior wall of the duodenum with exposure of the mucosal surface of the posterior wall, will occasionally reveal an ulcer which is the cause of previously considered unexplained bleeding. This point has been emphasized by Balfour.

It is considered that gastric ulcers bleed in approximately 25 per cent of all cases. In the present series, gastric ulcers accounted for 43 (71 per cent) of the 602 cases. This, compared to 59 per cent for duodenal ulcers, indicates that bleeding duodenal ulcers occurred eight times as frequently as bleeding gastric ulcers in the present series. This approximates the percentage incidence of the 2 lesions.

The mechanisms of production of bleeding in gastric ulcers are similar to those already considered for duodenal ulcers. Also, a gastric ulcer undergoing malignant change almost invariably causes occult blood in the stools and gastric content, whereas benign ulcer, as a rule, leads to occult bleeding in periodic cycles, coincident, apparently, with the activity of the ulcer.

This series includes 92 cases in which the hemorrhage leading to hematemesis was found to be due to secondary peptic ulceration. It is an interesting fact, as has been previously pointed out by one of us (Dr. Rivers), that in cases of peptic ulcer in which there has once been hemorrhage there seems to be a special tendency to occurrence of bleeding, if recurring ulcers or reactivation of such ulcers occur following medical or surgical treatment. If, for instance, an ulcer exhibiting hemorrhagic tendencies is present in the duodenum, for the cure of which short-tracking operations were performed, there seems to be a special liability on the part of the symptoms if they

recur, to include further bleeding. Surgical treatment, therefore, in cases in which there is hemorrhage should include, whenever possible, the excision of such lesions.

Our present series includes certain cases in which the duodenal ulcer was excised and in which a second ulcer exhibiting hemorragic tendencies appeared in the duodenum. A few cases have also come under our observation in which gastric ulcer was found to have been the cause of bleeding, and in which, after excision of the ulcer and gastro-enterostomy, further hemorrhage took place. This may be found to be due to a second ulceration in the stomach, which was too small to be readily recognized at the time of the first operation. It is therefore essential to explore the entire stomach, even though one ulcer is found which might be held responsible for symptoms in a given case.

Gastrojejunal types of ulceration are likely to be complicated lesions, the two types of complications most frequently encountered being hemorrhage and deep penetration or even subacute or acute perforation. Hemorrhage occurs in 34 per cent of the cases of gastrojejunal ulcer. Occasionally, hemorrhages arise from shallow, mucosal erosions surrounding the gastro-enteric stoma. At other times, extensive lesions about or below the stoma are found, from which extensive bleeding occurs. Gastrojejunal ulcers are a little more likely to cause bleeding by bowel than to produce hematemesis, and the bleeding is likely to be slow, so that long-continued oozing may occur before the complication of the bleeding is suspected.

The diagnosis of ulcer is generally simple since, in the majority of cases, a good history of peptic ulcer is obtained. Careful questioning may elicit such a history in an additional number of cases in which it at first appeared that there was no history of such a complaint. It is unusual for the bleeding to occur without any preceding gastro-intestinal disorder. Hinton<sup>10</sup> pointed out that the cases of acute hemorrhage that proved fatal in spite of conservative treatment occurred in cases in which the history was negative or short. This observation deserves further consideration. The fatal cases in the present series were so few that denial or affirmation cannot be made. Roentgenologic study, when the bleeding has ceased, will usually localize the lesion in the stomach or duodenum. Such localization by history alone is, as a rule, unsatisfactory.

The differential diagnosis of the various recurring or reactivated duodenal ulcers offers a study which, in itself, is sufficiently extensive to warrant separate consideration. We shall mention here merely a few of the fundamental facts regarding diagnosis. In recurring ulcera-

<sup>10</sup> Hinton, J. W. Bleeding Gastric and Duodenal Ulcers. Report of Fifty-Two Cases, *Ann Surg* **93** 949 (April) 1931.



tions, if the secondary lesion is in an area approximating the first lesion, the symptoms including the site of pain are usually similar to those experienced with the original lesion. If recurrence takes place in the duodenum, the symptoms generally are almost exactly like those experienced previous to the first operation. These principles apply also in cases of recurring gastric ulcer in which secondary ulcer develops in an area approximating the original area. The syndrome of a gastrojejunal ulcer usually includes pain farther to the left and considerably lower than that experienced with the original ulcer in the stomach or duodenum. Roentgenologic examination still offers great help in the localization although, obviously, in recurring ulcers of the duodenum, its efficiency is not so great as in the case of the original lesion. In such instances the history, however, is usually sufficiently definite so that its careful study will permit of a diagnosis without great difficulty.

#### HISTORY OF ULCER ROENTGENOLOGICALLY NEGATIVE, NOT EXPLORED

This group, which includes 22 cases, seems of sufficient importance to be considered separately. A positive diagnosis was not made in these cases, although there seems little doubt that a diagnosis of peptic ulcer usually would have been justifiable. Although it is not an infallible rule, it is generally true that history which includes data on hemorrhage and indigestion, with characteristics of ulcer, is diagnostic of an intrinsic, ulcerating or localized inflammatory gastroduodenal lesion, regardless of the absence of confirmation by the roentgen rays. Such lesions may be malignant, but more often they are benign.

The cases in which exploration was done include many in which the roentgenologic examination for a lesion was not conclusive or failed to show any deformity, and yet operation was advised because the symptoms seemed sufficient to make exploration advisable. In certain such cases operation was not advised because the history included evidence suggesting only trivial amounts of bleeding or a mild type of indigestion. In other cases, there was a history of rather brisk hemorrhage, which had occurred months or even years prior to consultation at the Mayo Clinic, and in these merely a mild type of indigestion persisted. Operation was not advised in others because of the presence of some serious intercurrent disease, so that operation would have been undertaken at considerable risk to the patient.

There is still another group of cases in which operation was advised but refused by the patients. On several occasions, it has been pointed out by one of us (Dr. Rivers) that serious indigestion, which may be associated with hemorrhages, can be produced by shallow mucosal lesions with or without ulceration in the stomach, duodenum or about a gastroenteric stoma. One need only inspect such lesions in the operating room

to be convinced that roentgenologic evidence might be entirely lacking. In such cases there may be no lesion capable of producing a niche other than an erythematous, inflamed mucosal or submucosal area in which there may or may not be a few small, punched-out areas, and it is conceivable that these lesions would not produce direct roentgenologic evidence of their presence.

Kirklin<sup>11</sup> in describing the appearance of shallow duodenal lesions, stated that occasionally one could recognize such lesions by the extreme irritability of the duodenal bulb, even though there was no direct evidence of a fleck or a niche. The liability of such lesions to bleed is indicated by the fact that gastro-enteric hemorrhage occurred in 15 per cent of cases of duodenitis reported by one of us (Dr. Rivers) in 1931. There seems little doubt that these shallow inflammatory lesions go a long way toward explaining most of the so-called indeterminate cases of hemorrhage. It is probable that in many of the cases of so-called gastrostasis as described by Hale White and others, the hematemesis is due to such nonulcerating inflammatory lesions. If operation were undertaken during such hemorrhage or immediately following, there would be definite evidence, in most instances, of the presence of some such lesion if any other cause for the hemorrhage could not be demonstrated.

#### CARCINOMA OF THE STOMACH

Malignant lesions involving the stomach were found to be the cause of hematemesis in 12.6 per cent of all cases coming under our observation over a two year period. Although, undoubtedly, most carcinomas of the stomach are responsible for some bleeding, it is unusual that gross bleeding occurs. A careful investigation of the stool in most instances will reveal the presence of small amounts of occult blood, which are present rather consistently from day to day. The vomiting of blood in large amounts is, however, an extremely rare complication of carcinoma of the stomach. This symptom was present in only 1 per cent of a series of cases of gastric carcinoma. The amount of blood vomited is usually small and, because of its mixture with gastric content, it resembles coffee-grounds.

In many instances of gastric malignancy, the diagnosis cannot be made from careful evaluation of the history, and if the diagnosis is delayed until vomiting of blood occurs, the majority of these patients will have passed beyond that period when the surgical removal of such lesions is still possible.

The diagnosis of early carcinoma of the stomach is usually made by means of roentgenologic investigation. This method of examination is

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<sup>11</sup> Kirklin, B. R. A Roentgenologic Consideration of Duodenitis, *Radiology* 12: 377 (May) 1929.

*Course*—At operation, a myoma high on the posterior wall, near the cardiac portion of the stomach was found. The tumor was attached to the stomach by means of a pedicle. There was an ulcerated area on the surface of the myoma. The tumor was excised. Convalescence was without incident.

*CASE 2—History*—A man, aged 37, had had periods of pain in the epigastrium which came on two hours after meals. The period of pain would last for several weeks, and then for several months he would be entirely free from symptoms, which consisted of what he described as a dull, gnawing pain, which was relieved by eating. About eight weeks before consultation at the clinic, the pain became severe and lasted for a day or two. Five weeks before registration, he had had another episode of severe pain and shortly after this had felt nauseated and had vomited large amounts of dark, bloody material. He consulted his physician, who made a diagnosis of peptic ulcer and advised a regimen of milk and alkali. Since the institution of this type of treatment, the patient had been quite comfortable.

*Examination*—Examination disclosed slight tenderness in the epigastrium. There were no palpable masses. Estimation of gastric acids showed total acidity 62, and free hydrochloric acid 44, the amount expressed was 350 cc. The concentration of hemoglobin was 73 per cent, erythrocytes numbered 4,650,000, and leukocytes 7,600. There was no evidence of enlargement of the spleen or of disease of the liver. Roentgenologic investigation of the stomach and duodenum failed to show any definite evidence of abnormality. Because of the history, which included gastro-intestinal hemorrhage, operation was advised.

*Course*—A chronically diseased appendix and a small tumor of the duodenum were found. The pathologist reported this to be a myoma. It was assumed that the bleeding came from the tumor. The patient was examined two years after operation, and there had been no recurrence of the bleeding.

Benign tumors of the stomach and duodenum are rare, and they do not as a rule cause gross bleeding. The most common benign tumors involving the stomach and duodenum are polyps, adenomas, myomas, fibromas, hemangiomas and papillomas. The symptoms arising from these tumors may be of several types, for example (1) those caused by interference with normal mechanics of digestion, such as difficulties in proper emptying of the stomach or obstruction by tumors becoming impacted in the pylorus or the lumen of the bowel, and (2) those arising subsequent to severe anemia, which may be associated with these tumors. Balfour and Henderson,<sup>13</sup> in reviewing the symptoms in a series of benign gastric and duodenal tumors, felt that the most common and most significant sign of benign tumor of the stomach is anemia. They pointed out that, although benign tumors seldom bleed, if they do, the loss of blood may be extremely exhausting.

The pathologic changes in benign gastric and duodenal neoplasms leading to bleeding are variable and depend on the nature of the tumor. Polyps continually oozing small amounts of blood, because of superficial necrosis and sloughing, may lead to severe anemia which may be

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<sup>13</sup> Balfour, D. C., and Henderson, E. F. Benign Tumors of the Stomach, *Ann Surg* 85:354 (March) 1927. Benign Tumors of the Duodenum, *ibid* 89:30 (Jan) 1929.

recognized as secondary anemia or occasionally as anemia with a picture simulating primary (pernicious) anemia. It may be difficult to believe that severe anemia can be produced by such a small lesion, especially in the absence of manifest, gross bleeding. Rieniets<sup>14</sup> stated that bleeding in cases of gastric leiomyoma is characteristically periodic and profuse, and that it depends on deep ulcerations of the tumor. The larger the tumor the more readily does profuse hemorrhage occur. The pathogenesis of bleeding in cases of hemangioma is obvious.

Pyloric obstruction was found to be present in 10 per cent of the cases reported by Balfour and Henderson. In obstructed cases the tumors were found to be attached to the posterior wall of the stomach, and because of either a pedicle or redundant mucosa could occlude the pyloric canal. They pointed out that in certain instances, the indigestion associated with these tumors had definite characteristics of peptic ulceration. Preoperative diagnosis is made almost exclusively by fluoroscopic examination.

#### GASTRIC SYPHILIS

**CASE 3—History**—A man aged 27 stated that ten years prior to his visit to the clinic, he had vomited blood on one occasion. Eight years later, severe pain in the left upper part of the abdomen had developed which lasted for half an hour. It was necessary to relieve this pain by the use of morphine. He had been hospitalized for three weeks' observation, but a definite diagnosis was not made. At that time, he noticed black stools for a few days. Following this episode he was well for a period of one year, at the end of which time distress again developed in the epigastrium. This time the pain was not so severe, and he noticed much flatulence and a sensation of fullness in the epigastrium after meals. At intervals, he had pain in the left upper part of the abdomen, and on a few occasions there was some vomiting. His distress usually came on during or immediately following meals, and occasionally he vomited shortly after a meal.

**Examination**—Examination disclosed a palpable mass in the upper left part of the abdomen. The concentration of hemoglobin was 50 per cent, the erythrocytes numbered 3,950,000, and leukocytes 8,600. Estimation of gastric acids showed total acidity ranging from 36 to 96 and free hydrochloric acid from 16 to 76. The serologic test for syphilis was positive. Tests of hepatic function did not give evidence of retention of dye. The serum bilirubin was within normal limits. Roentgenologic examination disclosed an hour-glass stomach, and a diagnosis was made of gastric ulcer.

**Course**—Exploration revealed the presence of a gastric lesion which had all the characteristics of syphilis. There were several good-sized nodules in the liver, one of which was excised for diagnosis and proved to be inflammatory. There was fairly definite obstruction between the loculi of the hour-glass contraction, and gastrogastrostomy was performed. Subsequent to the operation, the patient was given intensive treatment for syphilis. There has been no evidence of recurrence of the hemorrhage.

<sup>14</sup> Rieniets, J. H. The Frequency and Pathologic Aspects of Gastric Leiomyoma, Proc. Staff Meet. Mayo Clin. 5:364 (Dec. 17) 1930.

Eusterman<sup>15</sup> recently reviewed a series of 93 cases of gastric syphilis. Regarding the association of hemorrhage in this connection, he said

Although I realize that there have been authentic reports of cases of severe gastro-enteric hemorrhage, including those of acute perforation, there are only five trustworthy instances of bleeding in this entire series. In two of these there was definite evidence of associated hepatic lobatum, and in the others, undoubtedly, syphilitic changes in the liver had taken place, as is the rule. This lesion might have played a considerable part in the production of the hemorrhage, as Chiari has pointed out. Obliteration of the arteries and veins in actual syphilitic gastric lesions and the tendency to fibrosis and atrophy, or to degeneration of the parenchyma, are undoubtedly large factors in preventing gross or occult bleeding. Hemorrhage is more characteristic of ulcer and carcinoma. In only fourteen cases was anemia present. This was of the secondary type and usually was not marked.

There is, of course, the possibility that, in the case reported here there was sufficient injury to the liver so that increased portal block with varices must be borne in mind as a possible explanation for the hemorrhage.

#### SUMMARY

Intrinsic gastroduodenal lesions, that is, peptic ulcer, gastric carcinoma, inflammatory processes and benign tumors, accounted for approximately 90 per cent of 668 cases of hematemesis.

The most common single lesion responsible for hematemesis is peptic ulcer, including duodenal, benign gastric and anastomotic ulcers, which comprised 85 per cent of the cases of hematemesis due to intrinsic gastroduodenal lesions.

Carcinoma of the stomach was the etiologic factor in only 12.6 per cent of the cases of hematemesis. Hematemesis usually appears like coffee-grounds in gastric carcinoma, and the bleeding is rarely profuse. Massive hematemesis occurs in only 1 per cent of cases of gastric carcinoma.

Localized or diffuse areas of inflammatory reaction of nonspecific character in the stomach, duodenum or surrounding a gastro-enteric stoma may lead not only to symptoms suggestive of peptic ulceration but to hemorrhage, and yet such areas may not produce sufficient abnormality in the contours or functions of these organs to be recognizable roentgenologically. Such an inflammatory area may be one of the underlying causes of bleeding previously described as gastrostasis by Hale White and others.

Benign tumors of the stomach and duodenum and gastric tuberculosis and syphilis are rare causes of hematemesis and their diagnosis usually depends on roentgenologic or surgical observation.

The mechanism of bleeding of the various intrinsic gastroduodenal lesions causing hematemesis has been considered.

<sup>15</sup> Eusterman, G. B. Gastric Syphilis, J. A. M. A. 96:173 (Jan. 17) 1931.

# SICKLE CELL ANEMIA

## REPORT OF A CASE

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Sickle cell anemia since its description by Herrick<sup>1</sup> in 1910, has become established as a well defined disease entity. The clinical picture is so distinctive that a tentative diagnosis of the condition can be made from the history and physical signs before the examination of the blood is completed. While the disease is relatively frequent in some sections of the country, perhaps on account of its familial tendency and the drawing power of the more celebrated clinics nevertheless it is rare in this vicinity the only other case in Houston brought to my attention besides the one to be reported having been published by Milliken<sup>2</sup> in 1928. Sydenstricker<sup>3</sup> reported a ratio of 1 case to every 400 Negro patients seen in his clinic but the incidence in this locality is almost certainly not so high as I and my associates have been constantly on the lookout for this type of anemia with only the modicum of success indicated. The sickle cell trait however, maintains practically the same percentage here as elsewhere, showing but little variation in its national distribution if one is to judge by the few reports that have been published. In 150 Negro workers studied by me<sup>4</sup> the incidence was found to be 6.67 per cent, this number was subsequently increased to over 200, with an incidence of 6.5 per cent. Some confusion has arisen through want of a uniform classification of the subject. Sydenstricker objected to the classification proposed by Huck (symptomless, mild and severe) on the grounds that the so-called symptomless cases are in reality not symptomless, and suggested that the cases be designated as latent or active. However, as pointed out by Hahn,<sup>5</sup> it would seem inconsistent with present usage to say that a person who is not now anemic, and has never evidenced any tendency to be anemic, has a case of latent anemia. He therefore used the term sickle cell trait in referring to the condition in

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1 Herrick, J. B. Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia, *Arch Int Med* **6** 517 (Nov.) 1910

2 Milliken, Gibbs. *M Rec & Ann* **22** 49 (March) 1928

3 Sydenstricker, V. P. Sickle Cell Anemia, *South M J* **17** 177 (March) 1924

4 Brandau, G. M. *Am J M Sc* **180** 813 (Dec.) 1930

5 Hahn, E. V. *Am J M Sc* **175** 206 (Feb.) 1928

which sickling occurs in most blood films, or on the other hand a reduction in the erythrocyte count and no sickling, or a moderate previous hemolytic attack. The following classification, which is a part of those already outlined is offered, and with the advantage that in cases in which sickling takes place can be definitely assigned to some subdivision or subdivision according to the present knowledge of the subject.

I Sickle cell trait, healthy persons with sickling in vitro

II Sickle cell anemia

1 Latent, healthy persons who are subject to recurrent periods of active sickle cell anemia

2 Active

(a) Mild, slightly or moderately anemic patients with sickling in vitro or both in vivo and in vitro

(b) Severe, patients with severe grades of anemia with sickling in vivo and in vitro

The word healthy is used in respect to sickle cell anemia and not exclude other unrelated conditions.

The literature on sickle cell anemia has been rather sparse, as is shown by reference to the *Quarterly Cumulative Index Medicus*, and, aside from the case reports of Huck<sup>6</sup> and of Sydenstricker,<sup>7</sup> the number of clinical studies has been few. On account of the comparative rarity of the disease and the points of especial interest presented by my case, it seems justifiable to describe the findings in some detail.

#### REPORT OF A CASE

*History*—I H, a Negro, aged 22, tall, poorly developed and poorly nourished, was admitted to the Jefferson Davis Hospital on Oct. 28, 1931 (in the service of Dr. F. H. Kilgore), with the diagnosis of acute endocarditis and tertiary syphilis. On admission his complaints were (1) shortness of breath, (2) swelling of the feet and ankles, (3) general weakness, (4) increased frequency of urination, (5) dull pain throughout the entire chest and (6) ulcers on the right leg.

The present illness began five months before admission when the patient was troubled with swelling and aching of the wrist and ankle joints. He called this trouble rheumatism. Pain in these joints continued and grew worse, his knees became sore and painful but did not swell, and three weeks before admission he was confined to bed with shortness of breath, edema of the feet and ankles and pain in the chest. The sores on his leg, however, had been present for eighteen months or longer. He had not felt well since the first of the year and had been having fever all this time. The urine had been highly colored, and at times there was burning on urination. Sometimes his symptoms were intensified when the urine was highly colored.

The patient's mother had told him that he was a normal, healthy baby until he was 9 months of age, but that since then he had never been in robust health. His

6 Huck, J. A. Bull. Johns Hopkins Hosp. **34**: 335 (Oct.) 1923.

7 Sydenstricker, V. P. Sickle Cell Anemia, J. A. M. A. **83**: 12 (July 5) 1924 (footnote 3).

birth and childhood were of marked and unusual incident, but he was unable to state by what onset of symptoms antedated the period of weaning. He had had a whooping cough when a child, but had escaped the other infectious diseases of childhood. When he was a small boy he suffered from rheumatism, and he stated that he had been jaundiced in his life. When about 13 years of age he began to have "stitches" in his legs and these continued for several years finally healing at the age of 14. The year before examination he had an attack of severe pain in the abdomen which lasted about a week, and which was not accompanied by diarrhea or vomiting. He was not attended by a physician at that time so no diagnosis was made. He said that he had never had a venereal infection, he had never been married, but he considered his libido and sexual power to be normal when he was not acutely ill.

His father was living and well. His mother died of a miscarriage when he was 5 years of age. One brother and three sisters were living and well. Several young ones had died in infancy. No history of familial disease could be elicited, especially there had been no rheumatism, jaundice or disease similar to the patient's illness. All other members of the family as far as the patient knew or could remember had been strong, robust people.

*Physical Examination*—The patient was a somewhat emaciated adult Negro, lying quietly in bed but evidencing some distress from dyspnea and exhibiting the harassed facies of the person with cardiac decompensation. His extremities were long in proportion to his body. The skin was dry and intensely black. The palms and soles and mucous membranes showed a distinct pallor. Although tall, he was of slight build and his muscles were poorly developed. There was a generalized lymphadenopathy, the cervical, axillary, epitrochlear and inguinal nodes being palpable on both sides. The patient appeared somewhat younger than his stated age of 22 years, resembling more a youth of 17 or 18. The blood pressure was 130 systolic and 45 diastolic.

The scalp was covered by a thick growth of short, kinky hair, although the beard was scanty. The eyes were prominent, showing slight exophthalmos, but the most remarkable ophthalmic finding was a peculiar greenish hue of the sclerae. The palpebral conjunctivae exhibited marked pallor. The external ocular movements were normal, and von Graefe's sign was negative. The teeth were in fairly good condition but poorly kept. The right tonsil was large, the left of normal size, the mucous membranes were pale.

Pulsations synchronous with the heart beats were observed on both sides of the neck. The lymph nodes were enlarged enough to be palpable, but there was no evidence of enlargement of the thyroid.

There was moderate scoliosis, with resultant distortion of the chest. There was also a slight, well rounded kyphosis. A diffuse impulse could be seen and felt over the cardiac area with each heart beat. Dulness extended 2 cm. beyond the nipple line on the left and 2 cm. beyond the external border of the sternum on the right. On auscultation, a to-and-fro murmur was heard over the whole precordium. The pulmonary second sound was accentuated and distinctly louder than the aortic second sound. The heart beat was regular and rapid. The area of hepatic dulness was increased upward. The lungs, as well as could be judged with the thoracic deformity, expanded about equally. Tactile and vocal fremitus were increased over the left lower lobe, where also there was dulness on percussion and increased vocal resonance. Moist râles could be heard in both bases, with bronchial and broncho-vesicular breathing over the left lower lobe.



The abdomen was soft. The spleen was not enlarged. The lower border of the liver could be felt as a fingerbreadth below the right costal margin and the clavicular line, and the tip was distinctly felt.

The arms and legs were contracted. Both the lateral and the medial malleoli of the left leg were the scar of a healed ulcer. On the anterior surface of the right leg there were two ulcers, one about 6 cm in diameter, the other about 4 cm. These ulcers were circular and shallow and had clean bases with only a small amount of discharge. The skin over the lower half of the leg and over the feet and ankles was hard and wrinkled. There was a moderate amount of edema of the ankles.

The genito-urinary organs appeared normal but the pulse rates had a normal distribution.

The reflexes were normal. Mentally the patient was although his mind was alert and active.

*Laboratory Examination*—Oct 28, 1931. Urinalysis on the day of admission showed a straw-colored urine with a specific gravity of 1.014, an alkaline reaction and a trace of albumin. Microscopically amorphous urates and occasional epithelial cells were seen. Examination of the blood on the same day revealed hemoglobin 40 (Sahli), color index, 1, erythrocytes, 2,000,000, leukocytes, 14,400, poikilocytes, many, anisocytosis, marked, coagulation time three minutes, and bleeding time two minutes and ten seconds. The polymorphonuclear neutrophils were 72 per cent, small lymphocytes, 28 per cent, and normoblasts, 2 per hundred leukocytes. There was marked achromia.

Oct 29, 1931. The Wassermann and the Kahn tests were negative on the following day.

Oct 30, 1931. The blood poikilocytes were many, and anisocytosis was marked, there were 3 normoblasts per hundred leukocytes.

Oct 31, 1931. Examination of the spinal fluid showed it to be clear and colorless, with globulin not increased, cell count of 3, negative Wassermann reaction, and a mastic reaction of 000000000000.

Nov 4, 1931. There was no reaction to the van den Bergh test. Schlesinger's test for urobilin gave negative results, and the reaction for bile was negative. However, on November 6, both reactions were positive. At this time, the feces were negative for parasites and ova.

Nov 10, 1931. The urine was negative for bile on this day. Ehrlich's test for urobilinogen gave a cherry red reaction. The van den Bergh indirect reaction of the blood serum for bilirubin returned 0.487 mg per hundred cubic centimeters of serum.

Nov 13, 1931. Examination of the blood showed creatinine, 0.91 mg, sugar, 102.4 mg, urea nitrogen, 23.1 mg, and nonprotein nitrogen, 45.7 mg. The hemoglobin was 38 (Sahli), color index, 0.95, erythrocytes, 2,000,000, leukocytes, 16,800, poikilocytes, many, anisocytosis, marked, platelet count, 480,000, polymorphonuclear neutrophils, 84 per cent, small lymphocytes, 12 per cent, eosinophils, 1 per cent, basophils, 1 per cent, mononuclear neutrophils, 2 per cent and normoblasts, 4 per hundred leukocytes, achromia was marked.

Nov 14, 1931. On the following day the gastric contents showed free hydrochloric acid after an Ewald test meal.

Nov 15, 1931. The phenolsulphonphthalein test of kidney function showed first hour 25 per cent, second hour, 20 per cent with a total of 45 per cent. The fragility test revealed erythrocytes. Hemolysis of the patient's cells began in a tube containing 0.3 per cent of salt solution and was not complete in the last dilution of 0.28 per cent. Hemolysis of normal cells began in a tube containing 0.42 per cent of salt solution and was complete in one containing 0.34 per cent.

Dec 2, 1931 The total count of erythrocytes showed a population of 40 (Sahli), erythrocytes 2,100,000, leukocytes 6,000, polymorphonuclear neutrophils, and myelocytes, 50 per cent, small lymphocytes 36 per cent, and monocytes 4 per cent. Erythrocytes had marked chromatin.

Dec 4, 1931 The basal metabolic rate on December 4 was +8.

Dec 5, 1931 A chemical analysis of the blood by Dr. H. O. Nicholas of Rice Institute showed phosphorus 2 mg, phosphorus 53 mg, and chlorides as sodium chloride 37 mg per 100 centimeters of serum.

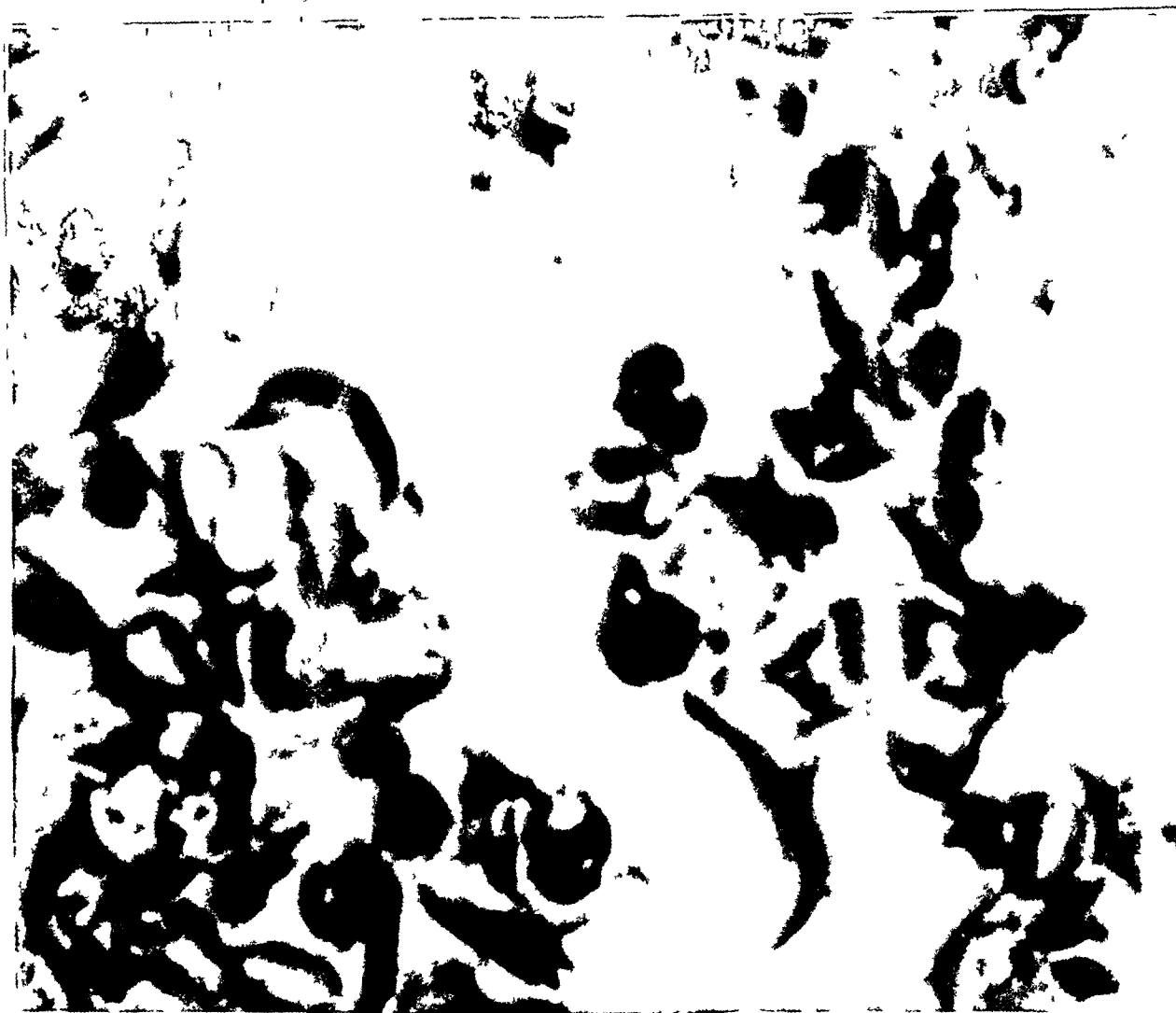


Fig 1—Dry stained smear showing sickle cells. Moist films after twenty-four hours exhibited a high percentage of drepanocytic forms.

Dec 9, 1931 The hemoglobin of the blood was 43 (Sahli), the erythrocytes were 2,550,000, leukocytes, 12,200, polymorphonuclear neutrophils, 74 per cent, small lymphocytes, 26 per cent, and there were many sickle cells.

Dec 17, 1931 The hemoglobin of the blood had changed to 50 (Sahli) and there were 2,300,000 erythrocytes.

Dec 21, 1931 A blood smear for reticulocytes showed 6.3 per cent.

Interpretation of the roentgenograms was made by Dr. B. T. Vanzant.

Oct 1, 1931 The chest x-ray shows a host of considerable deformity of the chest. The mediastinum is widened—indicating pericarditis with effusion. The lungs are normal, especially the base of the right lung is slightly hypostatic pneumonia.

Oct 31, 1931 A roentgenogram shows at this time an enormously dilated heart with hypostatic pneumonia in the right

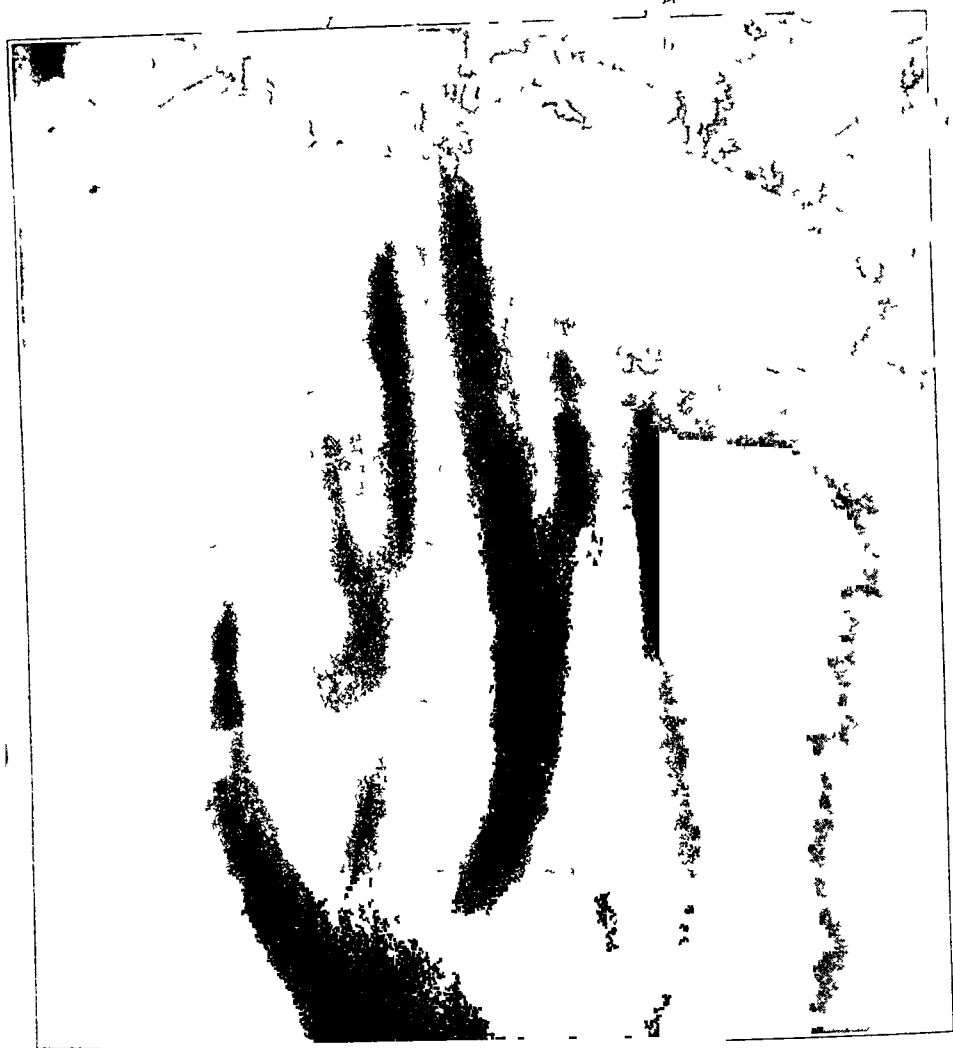


Fig 2—Roentgenogram of the chest showing the enormously dilated heart

Nov 19 1931 A roentgenogram of the skull on November 19 showed a moderate amount of striation in the parietal margin, numerous rounded areas of absorption near the vertex, suggesting pachymeningitis. The mossy, striated appearance between the two tables of the skull, the parietal region, is frequently observed in sickle cell anemia, but is not always present. The same appearance is encountered in numerous other conditions. The rounded areas of resorption are similar to those found in metastatic malignancy. The appearance differs slightly from that of metastasis, the margins being more clearly defined and the distribution corresponding more nearly to the area of the greatest frequency of the pachyomen bodies.

No. 931. Roentgenogram of the leg shows slight bowing of both tibiae, the middle of the femur is broken. The middle portion of the bone shows a large area of sclerosis and a distinct loss of density. The results of treatment are shown in the next figure.

Progress.—On admission, there was a pulse of 101 F. During the first two weeks in the hospital, the temperature varied between this point and 98.6 F, with occasional fever variation above or below these figures. In the third week, the temperature fell to 96 F, and toward the end of the fourth week, it had not come out into the normal range except for a two day flare-up reaching 100 F. Throughout the remainder of hospitalization, the pulse rate varied



Fig 3—Rounded areas of resorption can be seen in the occipitoparietal region. The striations between the tables of the skull which are present in the original roentgenogram do not show plainly in the reproduction.

between 100 and 128 until the third week, when it remained at 100, after which it fluctuated between 80 and 100 until the patient left the hospital. On entering the ward he was given a diet low in protein with the intake of fluid limited to 1,000 cc per day. Digitalis and ammonium nitrate therapy was instituted, and morphia was given to permit sufficient rest and sleep and to allay the pain. Fowler's position was used on account of the difficulty in breathing. The edema subsided rapidly, and dyspnea and pain diminished, so that after the first week the patient rested well though still complaining of some shortness of breath. The area of consolidation in the left lung cleared up as compensation of the heart was established, and the moist râles disappeared. Clinically, this was not pneumonia, but was produced by compression of lung tissue by the enormously dilated heart in the

same manner that the signs were produced in the present case. The hypostasis was no doubt the result of passive congestion and at the same time the patient was subjected to a harassing cough.

Although enlargement of the liver is an integral part of the syphilitic complication of sickle cell anemia, passive congestion due to heart failure was a sufficient cause to

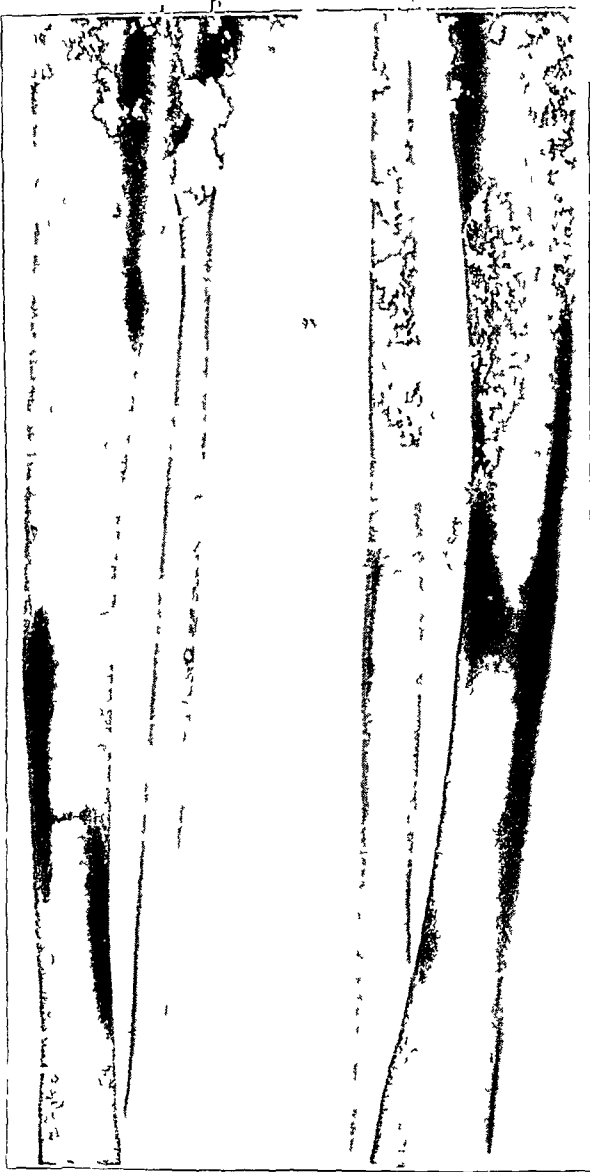


Fig. 4 - Roentgenogram of the bones of the legs showing the decreased density and splashing in the medullary portions. At this angle the bowing of the tibiae is not much in evidence.

account for the hepatic signs in this case, for as compensation was restored, the liver returned to normal size and the tenderness disappeared.

The ulcers on the leg were dressed with ammoniated mercury, U. S. P., and healed fairly promptly. Rest in bed, however, probably had more influence in obtaining this result than did the medicament employed.

I except a very small amount of solution of potassium iodide was begun on October 31. The weight of the rectal preparation was injected into the rectum twice every day for six days, and the latter was given in 15 minims (0.5 cc) three times a day. On November 20 fresh spleen was added to the patient's diet for as he spoken of it as a necessity in these advanced cases it seemed possible that splenic atrophy might prove a benefit. A soft diet with spleen was continued without significant improvement in the patient's condition until December 1 when spleen was discontinued and ventricular suction was ordered. The patient's weight was 15.5 kg on December 23, and as we were not permitted to observe the effects of the latter condition, splenectomy was considered and a decision made to do it.

On November 20 the notes on the patient's progress described a pericardial rub. Two days later the rub was still audible but much softer, and on the following day could not be heard. On November 9, the patient complained of partial inability to use his left arm. The next day he could use it better and after that he made no further complaint of this complaint. From November 28 to December 1 he had diarrhea. Bismuth and camphorated tincture of opium checked the diarrhea and the fever subsided. On December 7, he complained of burning on urination. On December 9 the blood pressure was 110 systolic and 70 diastolic. The remainder of the patient's stay in the hospital was uneventful. He improved slowly and without any marked change in the erythrocyte count.

#### COMMENT

In the history it is interesting to note that the age of onset was definitely placed at 9 months. The symptoms that the patient exhibited at that time could not be determined except that while formerly a healthy vigorous baby he then became sickly and had poor health. As he grew older the symptoms were typical of his disease. The periods of burning on urination and of highly colored urine did not, as in some cases, always coincide with exacerbations of the illness, and the paroxysm of this nature that he suffered while under observation was not marked by intensification of symptoms or by significant change in the blood count. Abdominal crises were less frequent than in many cases, the history of only one being elicited. Unfortunately I was not able to examine the blood of the patient's relatives who live in the country some distance away.

The slender build, youthful appearance and general lymphadenopathy are common findings in sickle cell anemia, and the green color of the sclerae, though not always present, is one of the diagnostic signs. It was thought that the bony deformities may possibly have been due to anemia in early life at a time when the osseous structures were normally soft and that they were made more so by the impoverished state of the blood. The roentgen appearance at the present time tends to support such a hypothesis and to rule out syphilitic osteoperiosteitis.

8 Yater, W. M., and Mollari, Mario. Pathology of Sickle-Cell Anemia, Report of Case with Death During "Abdominal Crisis," *J. A. M. A.* 96:1671 (May 16) 1931.

Extinct rickets as a cause of the lesion which necessitates largely there is of a forward bowing of the tibia and narrowening of the epiphyseal thickening of a distal tarsal.

#### MORRIS

Sickle Cell Anemia is a comparatively rare disease, still cell anemia is more common and apparently more widely distributed in classification of the conditions in which sickling of the red blood cells is offered in the hope that its removal will prevent the disease from existing. A case of sickle cell anemia is reported and compared on and the progress and treatment discussed. The case while typical presents some interesting individual features represented in the physical signs and in the roentgen and laboratory data. After the administration of splenic pulp, improvement occurred, but this was not marked enough to be significant. Treatment with mercury and iodides seemed to be of value but not specifically so. Study of the case was interrupted by the patient's departure from the hospital as improved.

# Book Reviews

*Diseases of the Coronary Arteries* (Myocarditis) By John C. Sutton, M.S., M.D., Associate Professor of Medicine, Northwestern University, and Lucius P. Luth, Ph.D., M.D., Formerly Professor of Pathology, Northwestern University. Chicago Cloth Price \$5.00. 164 pp., with charts and illustrations. St. Louis: C. V. Mosby Company, 1932.

Diseases of the coronary circulation have always been matters of great interest to physicians. Since the time of Forster and Jenner the amount of study and investigative work devoted to this subject has been tremendous. In this book Sutton and Luth have reviewed a vast amount of material and have covered the field in a way of great value to the reader. The mass of statistical data is included so rapidly and the book so abounds with references to the literature that the orderly discussion of the subject is somewhat obscured.

The first chapter is devoted to the symptomatology of heart failure. The authors rather apologetically touch on acute myocarditis and, indeed, it adds nothing to the book. The term itself is a difficult one to justify, and an attempt to deal with it in two scant pages is foredoomed to failure. The advisability of dealing with rheumatic fever under this heading and in one short paragraph is questionable. The section on chronic myocarditis is dealt with more adequately because it is definitely set off as the result of arteriosclerosis of the coronary vessels. While this definition may be questioned, it forms a limitation to the field of discussion.

The arrhythmias are well set forth although it is possible that the authors overemphasize the importance of the significance of ectopic contractions in patients over 40. They also totally disregard the possibility that auricular fibrillation may accompany minor pathologic changes, or may even occur in hearts apparently normal anatomically.

In the section on angina pectoris, the excellent work of the authors on the mechanism of the production of anginal pain is dealt with. This work is an exceedingly valuable contribution to the study of coronary disorders. It is unfortunate, however, that the authors have made no attempt to differentiate angina pectoris from anginal pain and have continued to confuse angina pectoris with coronary thrombosis. In one of the illustrative cases there is described under the head of angina pectoris an attack which lasted from Sunday until Tuesday. A few pages further on the same case is described as a coronary thrombosis which it proved to be at autopsy. Since Herrick separated from the heterogeneous mass of anginal pains the clinical entity now known as coronary thrombosis, one is able to select from the literature many cases described as angina pectoris that were undoubtedly thrombosis of the coronary artery. It would seem that the present knowledge of angina pectoris with its sudden onset and offset would permit one, with a little courage, to separate it from the remaining anginal pains and allow it to occupy a position of its own.

There is a full discussion of the causes of angina pectoris. The authors seem to doubt the presence of a vasoconstrictor mechanism in the coronaries, and yet inconsistently they later mention the vasoconstriction produced by nicotine, the probable vasoconstrictor action of digitalis and the vasoconstrictor responses elicited by the stimulation of certain nerves.

The symptomatology of coronary thrombosis is adequately described. In the section on physical examination of the heart, the physical findings are set down



and electrocardiography is discussed. Illustrations taken from the work of Croas and in the portrayal of the coronary circulation and in clinical pathology is well reviewed. The senior author adds to the scope of this section. A chapter is devoted to the drugs that influence the coronary circulation and the next chapter deals with the treatment of various types of myocardial failure.

There are numerous inaccuracies that keep the book from being the finished product that it should be. Euphyllin or metajodine, correctly called a theobromine compound, under the head of formalin, the authors discuss accumulation with some lack of clarity. In many places, brevity has been sacrificed for condensation.

In discussing the use of digitalis in auricular fibrillation, marked sinus arrhythmia is cited as evidence of an overdosage of digitalis. A respiratory arrhythmia has been noted in auricular fibrillation, but has been considered as evidence of an optimum dosage. The dose of some of the recommended drugs is given, and theocin and its sodium acetate are recommended in doses from 10 to 20 grains (13 to 19 Gm). Such doses have been known to produce convulsions.

The book contains many excellent illustrations, and its value is further enhanced by the use of numerous illustrative cases. The intrinsic value of the book more than offsets the portion open to possible criticism.

**Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung**  
**IV Tagung, gehalten zu Breslau am 9 und 10 März, 1931** Herausgegeben von Prof. Dr. Bruno Kisch, Köln. Price 15 marks. Pp. 242, with 53 illustrations. Dresden: Theodore Steinkopff, 1931.

The fourth session of the Deutschen Gesellschaft für Kreislaufforschung was devoted almost exclusively to a consideration of the experimental and clinical studies of digitalis that have been under investigation by German workers during recent years. This group of papers commends itself as a valuable contribution to the knowledge of digitalis. It is more than that, it is a concise presentation of the views now dominant in Germany regarding the indications for the use of digitalis, the proper methods of administration and its relative value as compared with its congeners, especially strophanthin. The latter drug is evidently much more widely used in Germany than in this country, and, one may add, it is better understood. As will happen in the transactions of any society, the papers differ from one another in glory. They are not all of equal value. Even so, this little volume is filled with information, stimulation and, in parts, fascination. The report of Priem on "Digitalistherapie" is excellent. It is a comprehensive review of the problems of present-day digitalis therapy, and is filled with suggestive and stimulating observations. Professor Schaffer's discussion of the arguments for and against the use of large doses of digitalis brings out the feeling that prevails in Germany regarding the Eggleston method of digitalis dosage. The point of his argument, which is emphasized by others, is essentially expressed in this sentence: "The central point of every course of treatment with digitalis is and remains individual dosage." His objection to the American method is that it does not meet the variable need for digitalis of the diseased heart. The use of strophanthin is evidently much better established there than in this country, and the indications for its use are more clearly defined, although the paper of Filip on the indications for the use of strophanthin is not altogether convincing. One of the longer articles is on the subject of "The Theory of the Digitalis Effect," by Otto Kraver. There are a few articles concerned with digitalis and electrocardiography, several on various other phases of digitalis investigation and others on subjects not related to digitalis. One of the most interesting of the latter is a long paper by Gruber on "Vascular Disease and Gangrene." This volume may be commended to all who are interested in the advances in the field of cardiac disease. It is exceptionally interesting and valuable.

**Traité de physiologie, normale et pathologique** Publié sous la direction de H. Roget, Professeur de physiologie à la Faculté de médecine de Paris et Léon Binet, Directeur de physiologie à la Faculté de médecine de Paris. Tome II. Alimentation et digestion. Par J. Bardet, G. Pettez, H. Ricard, Léon Binet, P. Garreau, P. Colonna, C. Delzenne, A. Desgrez, J. Gavet, R. Glenard, L. Halban, J. Harnet, V. Pi-Sunyer, M. Vaghi and E. Vollmann. Price, 100 francs. Pp. 300. Paris: Masson & Co, 1931.

The author, listed on the title page, has contributed to this volume on the following subjects: foods and nutrients, vitamins, thirst, the salivary gland, the stomach (chiefly secretion and digestion), the external secretion of the pancreas, absorption, bacteria and bacterial action in the digestive tract, mastication and deglutition and the movements of the stomach and intestine. A few of these discussions are excellent, especially those dealing with thirst, the digestive ferments and the effect of bacterial action but the volume as a whole is mediocre. The presentation consists chiefly of the ordinary facts previously established prior to five years ago with a striking lack of reference to work done since then. The findings of American investigators have received relatively little attention.

The type is readable, and the binding is excellent, illustrations are scarce. It is pleasant to note the brief historical reviews and the numerous references to the early workers in the various fields. These compensate in a measure for the omission of more recent material. The volume is of considerable value as a reference work.

**A Textbook of Laboratory Diagnosis with Clinical Applications for Practitioners and Students** By Edwin E. Osgood, M.A., M.D., Assistant Professor of Medicine and Biochemistry, University of Oregon Medical School, and Howard D. Haskins, M.D., Professor of Biochemistry, University of Oregon Medical School. Cloth. Price, \$5. Pp. 475. Philadelphia: P. Blakiston's Son & Co., 1931.

This splendid textbook is an outgrowth of an outline which has been used for years in teaching laboratory diagnosis at the University of Oregon Medical School. The subject matter has been divided into two natural divisions. Part 1 is a consideration of that body of knowledge which the practitioner must have available at the bedside of the patient. Part 2 is a consideration of the knowledge necessary for use in the laboratory.

The subject matter has been correlated by systems for practical purposes and to stimulate interest and to permit the person interested either in technique or in interpretation to study as a connected whole the phase of the subject that is of greater interest at the moment.

At the beginning of each chapter in part 1, there is a brief resume of the essential anatomy, physiology, biochemistry and pathology of the system under discussion. Source references are given in the footnotes throughout the book. The illustrations, many of which are in color, are excellent, and there are numerous tables and charts. In addition to the standard type of index, there is an index by diseases which enhances the value of the work as a handy reference volume.

This textbook is so thorough, clear and practical that it should rapidly become one of the "pets" in every student's library; also, the reviewer has not found a more suitable work for rapid review or ready reference for the busy practitioner.

**Guide to Radiologic Diagnosis in Heart Disease** By Geza Nemet, M.D., with the aid of the Committee on Research of the Heart Committee. Paper. Price, 35 cents. Pp. 33, with 31 illustrations. New York: New York Tuberculosis and Health Association, 1931.

**Criteria for the Interpretation of Electrocardiograms** By Arthur C DeGraft, M D with the aid of the Committee on Research of the Heart Committee Paper Price, 35 cents Pp 19, with 37 illustrations New York New York Tuberculosis and Health Association, 1931

These two pamphlets constitute a plea for standardization in cardiac diagnosis. The first pamphlet describes the technic of radiologic examination, what may be learned from radiologic examination and, equally important, what may not be determined. It is of equal value to the radiologist and the clinician. Many diagrams depicting the changes that accompany various disorders of the heart add greatly to the value of the work.

The second pamphlet should be entitled "Criteria for the Description of Electrocardiograms." Correctly enough, it does not consider interpretation in the sense that the fundamental cause of the electrocardiogram is discussed. Fifty key numbers are given which may be used to describe the various types of electrocardiographic curves. These cover all of the usual, and many of the unusual, graphs. Illustrative electrocardiograms are included.

The authors express the hope that both volumes may lead to more uniformity in the terms of cardiac diagnosis. Some such medical *esperanto* is surely needed and these pamphlets constitute a step in the right direction.

**Pain in the Pleura, Pericardium and Peritoneum A Clinical Study** By Joseph A Capps, M D, with the collaboration of George H Coleman, M D With an Introduction by Anton J Carlson, M D, Ph D Macmillan Medical Monograph Series Price, \$3 Pp 99 New York The Macmillan Company, 1932

This monograph consists of a description of concise experiments in the production of pain in the pleura, pericardium and peritoneum with accurate localization of direct and referred pain. The localization is charted and described. In addition, there are clinical reports with case examples of pain, the typical reference of which is explained by the authors' experimental results.

The experimental work is objective, and the experiments themselves are clear-cut and conclusive. The book is valuable for its physiologic and anatomic explanation of referred pain. Its clinical application is one of almost daily experience, the contents deserve the widest dissemination among students and practitioners.

THE SPECIFIC DYNAMIC ACTION OF PROTEIN  
IN PATIENTS WITH PITUITARY DISEASE

MARSHALL N FULTON, MD

AND

HARVEY CUSHING, MD

BOSTON

In the extensive literature on the specific dynamic action of food there have appeared a number of articles relating to the effect of the endocrine glands on this feature of metabolic activity. Experimental studies have led to varied conclusions as to the rôle played by the glands of internal secretion in altering the specific dynamic response to food. Foreign investigators in particular have reported finding this response diminished or completely absent in patients with diseases of the thyroid or pituitary gland.<sup>1</sup> In this country Baumann and Hunt,<sup>2</sup> Foster and Smith<sup>3</sup> and others have noted an abnormal specific dynamic response immediately following the administration of dextrose or amino-acids in rabbits and rats deprived of their thyroid or pituitary glands. Some of the workers, notably Kestner, Liebeschutz-Plaut and Schadow,<sup>4</sup> and Foster and Smith<sup>5</sup> have reported an increase in the specific dynamic action when preparations of pituitary gland were administered to normal persons, to patients with pituitary disease or to hypophysectomized animals.

An opposing view, however, championed by Lusk<sup>6</sup> supported by his own work and the observations of Du Bois,<sup>6</sup> Aub and Means,<sup>7</sup> Noid and

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1 Liebesny, P. Die spezifisch-dynamische Eiweisswirkung, *Biochem Ztschr* **144** 308, 1924. Plaut, R. Gaswechseluntersuchungen bei Fettsucht und Hypophysenkrankungen, *Deutsches Arch f klin Med* **139** 285 (May 23) 1922. Serejski, M., and Jislín, S. Endokrine Störungen und spezifisch-dynamische Eiweisswirkung, *Ztschr f d ges exper Med* **69** 321, 1930.

2 Baumann, E J., and Hunt, L. On the Relation of Thyroid Secretion to Specific Dynamic Action, *J Biol Chem* **64** 709 (July) 1925.

3 Foster, G L., and Smith, P E. Hypophyseal and Replacement Therapy in Relation to Basal Metabolism and Specific Dynamic Action in the Rat, *J A M A* **87** 2151 (Dec 28) 1926.

4 Kestner, O., Liebeschutz-Plaut, R., and Schadow, H. Spezifisch-dynamische Wirkung, Hypophysenvorderlappen und Fettsucht, *Klin Wchnschr* **5** 1646 (Sept 3) 1926.

5 Lusk, G. The Specific Dynamic Action, *J Nutrition* **3** 519 (March) 1931.

6 Du Bois, E F. Clinical Calorimetry. XIV Metabolism in Exophthalmic Goitre, *Arch Int Med* **17** 915 (June) 1916.

7 Aub, J C., and Means, J H. The Basal Metabolism and the Specific Dynamic Action of Protein in Liver Disease, *Arch Int Med* **28** 173 (Aug) 1921.

Deuel,<sup>8</sup> Gaebler<sup>9</sup> and Artundo,<sup>10</sup> holds that the endocrine glands have no direct bearing on the specific dynamic action. The present study, though conducted at the beginning in no attempt to take sides in this argument, has supplied evidence in support of Lusk and others so far as pituitary disease in man is concerned. It is published to show that patients with acromegaly or hypopituitarism and those with cerebral tumors either in the region of the pituitary gland or elsewhere have, following a protein-rich meal, a specific dynamic reaction which is well within the range of normal limits.

The first recorded observation on the basal metabolic rate in experimental hypopituitarism in animals (dogs) was made in 1912 by Dr John Homans of this hospital in collaboration with Dr Francis Benedict.<sup>11</sup> On the opening of the hospital a year later (1913), a metabolism laboratory was put in operation by Dr Walter M. Boothby, and it has been customary since that time, as part of the routine examination of patients with pituitary disorders, as often as possible, to record their basal metabolism before and after operation, if operations were performed. It was soon learned that patients with hypopituitary states associated with chromophobe adenomas had a low rate, and that patients with acromegaly had an elevated rate, as recorded in particular by Davidoff and Cushing.<sup>12</sup>

The present observations came to be made in conjunction with the work of Putnam, Benedict and Teel on experimental acromegaly in dogs.<sup>13</sup> As new lots of anterior pituitary lobe extract were being prepared, the laboratory workers were in quest of a test whereby the potency of any given preparation could be established without waiting for the time-consuming growth effect on the experimental animal. The work of Foster and Smith<sup>2</sup> had shown that the specific dynamic action, found wanting in hypophysectomized rats, was present after these animals were given both anterior and posterior lobe extracts. This

8 Nord, F., and Deuel, H. J., Jr. *Animal Calorimetry* XXXVII The Specific Dynamic Action of Glycine Given Orally and Intravenously to Normal and to Adrenalectomized Dogs, *J Biol Chem* **80** 115 (Nov) 1928

9 Gaebler, H. *Animal Calorimetry* XXXVIII The Specific Dynamic Action of Meat in Hypophysectomized Dogs, *J Biol Chem* **81** 41 (Jan) 1929

10 Artundo, A. Action dynamique specifique chez les chiens hypophysoprives, *Compt rend Soc de biol* **106** 139 (Jan 23) 1931

11 Benedict, F. G. and Homans, J. The Metabolism of the Hypophysectomized Dog, *J M Research* **20** 409, 1912

12 Cushing, H. and Davidoff, L. M. *Studies in Acromegaly* IV The Basal Metabolism, *Arch Int Med* **39** 673 (May) 1927

13 Putnam, T. J., Benedict, E. B. and Teel, H. M. *Studies in Acromegaly* VIII Experimental Canine Acromegaly Produced by Injection of Anterior Lobe Pituitary Extract, *Arch Surg* **18** 1708 (April) 1929

suggested to Dr Teel that if patients with pituitary disease were given the "unknown" anterior lobe extract there would be an alteration in their metabolic response to a protein meal. This phase of the work did not afford the desired results, but it initiated the present study of the specific dynamic reaction in the group of patients with pituitary disorders. The work at the start was under the supervision of Dr John Fulton.

#### MATERIAL

The eighty-two persons studied have been divided into five groups. Fourteen of them had outspoken acromegaly, which in four instances was verified by operation and shown to be associated with a chromophil adenoma. There were seven patients with what has been termed "fugitive" acromegaly<sup>14</sup>. Thirty-two others had the syndrome of pituitary insufficiency and were found to have a chromophobe adenoma. The remaining twenty-nine patients we have divided into (a) those with nonadenomatous tumors secondarily affecting the pituitary body and classified as patients with parhypophyseal tumors, and (b) those with tumors, or suspected tumors, not in juxtaposition to the gland. The latter group may in some degree serve as controls.

#### METHODS

This study was in no wise an attempt to determine the total heat effect produced by a fixed meal. A recent very comprehensive account of the specific dynamic action of food in abnormal states of nutrition by Strang and McClugage<sup>15</sup> notes in detail the factors which will determine the accuracy of a study purporting to show the heat effect of food. These authors confess that their "standards of admissibility" are rather exacting. We, however, were interested not so much in observing the precise minor changes in metabolism of a small group of patients as in noting in a larger group the presence or absence of a rise in metabolism after food and the extent of that rise during four hours. Thus, in many instances trial basal metabolism tests were not made preceding the test—a fact which means that the "base line" of the curves of increased metabolism may in some cases be open to question. Since tests were discarded which were grossly out of keeping with previous basal determinations or with the clinical observations on the patient, we do not feel that the figures would be greatly changed had "base line" observations been made to ascertain a constant level of basal metabolism before carrying out the test<sup>16</sup>.

Again, the metabolism was determined for only four hours following the ingestion of the meal. In fact, at the outset readings were made only at one and one-half and two hour intervals until it was appreciated that the peak of the heat rise would frequently be missed in such a short time. These cases are included since they show at least the presence of a heat response to food, though not necessarily the maximum one.

14 Bailey, P., and Cushing, H. *Studies in Acromegaly*. VII. The Microscopic Structure of the Adenomas in Acromegalic Dyspituitarism (Fugitive Acromegaly), *Am J Path* 4: 545 (Nov.) 1928.

15 Strang, J. M., and McClugage, H. B. The Specific Dynamic Action of Food in Abnormal States of Nutrition, *Am J M Sc* 182:49 (July) 1931.

16 In this connection one may note that the average total calories per hour in the "unacceptable" cases of Strang and McClugage's series do not differ greatly from the average of the other groups.

The tests were carried out as follows. Fourteen hours after the last meal the basal metabolism was determined indirectly by the Benedict-Roth spirometer with the patient in bed. During this and subsequent determinations his movements were restricted, and he was required to remain perfectly quiet. The basal metabolic rate was taken as the average of two six minute tests which varied from each other by not more than 3 or 4 per cent. The patient was then given 200 Gm of broiled chopped beef with which he was allowed 100 cc of water. Determinations were made again at one, two, three and four hours following this meal. Between tests the patient remained quiet in bed but was allowed to read.

#### METHOD OF TABULATION

The results are shown in tabular form in tables 1 to 5. The metabolism determinations have all been expressed in terms of the percentage variation from normal according to the surface area standards of Aub and Du Bois. This method of tabulation is adopted rather than total calories per hour because it is in common use and appears to us to be the method easily understood. In column 8 of each table are given the basal metabolic rates determined either on the day of the test meal or on days prior to or subsequent to this day. In the next four columns are listed the metabolisms taken at hourly intervals following the ingestion of beef-steak, and expressed in the same manner as the basal rate. The figures in column 13 are a numerical expression of the relation to the basal metabolism of the peak or highest metabolism reached following the test meal. They, therefore, represent the "percentage" increase over the basal "rate," and are derived by dividing the highest increase in metabolism by the basal metabolism. Thus, in patient 1 of table 1, the basal metabolism was 42.3 calories per square meter per hour, which is 107 per cent of normal for a man, aged 28 (39.5 calories), and is therefore expressed as +7. The highest metabolism reached was 53.8 calories per square meter per hour, which is 136 per cent above normal or +36. The increase may be expressed then either as  $53.8 - 42.3 = 11.5$  calories or as  $36 - 7 = 29$  "points."

Reducing this to percentage increase above the basal rate, we get  $\frac{11.5}{42.3}$ , or  $\frac{29}{107}$ , or 27.1 per cent. As may be seen from the tables, the peak of the rise in metabolism occurred at various time intervals following the test meal, which is a common finding in the measurement of the specific dynamic action. As noted previously, the tests which ran for only one and one-half or two hours are not a true index of the effects of the meal, but for the purposes of comparison they have been included.

Strang and McClugage<sup>15</sup> have pointed out that there are several technical objections to this method of expressing the fluctuations in metabolism. These points deal with (1) the height of the maximum rate or peak, (2) the numerical value of the basal rate and (3) variations in body surface. In a study of the total heat effect of a meal, one must take account of the extra calories produced throughout the entire time the meal exerts an influence on the metabolism. Thus a sharp rise during any single hour to an abnormally high peak will not serve as an index of the total effect. The true indication must consider the rise at each hour throughout a period of eight hours, or, as Strang and McClugage have expressed it, the total area of the curve of increased calories. For the purposes of this present study, however, we were concerned with the presence and extent of the rise at whatever time it occurred and have thus chosen the highest point as the indication of the specific dynamic action, realizing that it is not a complete expression of the total effect of the meal. Stating that for a given person this figure was 27.1 per cent, we mean a maximum rise of 27.1 per cent over his resting or basal level occurring at a definite time during the test, i. e., at the end of one, two, three or four hours.

It is obvious that since this figure is derived from a basal level that may be either above or below a fixed average, it will be significantly influenced by the numerical value of that basal level. Thus, in a patient whose basal metabolism is  $-20$ , a rise of 10 calories per square meter per hour will result in a higher percentage increase than if his basal metabolism is  $+20$ . An analogy may be drawn to a stock market transaction. If a stock which is bought at \$60 rises 40 points the profit will be twice that of a stock purchased at \$120 with a similar rise in value. One must keep these points in mind in comparing the figures for the chromophobe group in which the basal metabolism was below normal in all but four instances with those of the acromegalic group in which the basal rate commonly was elevated. In similar manner, the smaller the surface area the greater will be the percentage increase when the figures are in terms of calories per square meter per hour.

As a matter of fact, it makes little actual difference whether the results of the test are expressed in the percentage above and below normal according to calories per square meter per hour or as total calories per hour. For instance, in table 1, case 1, with a surface area of 1.92 square meters, the specific dynamic rise by the one method is 27.1 per cent, by the other 27.6 per cent. In case 3 with a surface area of 1.7 square meters, the figures by the two methods of calculation are 25.9 compared with 26. For the purpose of record, the height, weight and surface area have been noted in the tables from which, if desired, the total calories per hour can be readily calculated for purposes of comparison. The reader is referred to the article of Strang and McClugage for a fuller discussion of what they term artificial influences on the calculations in a study of this type.

## RESULTS

1 *Acromegaly (Hypopituitarism)* — As noted earlier in the paper, the eighty-two patients have been divided into five groups according to the diagnosis. In table 1 are listed the findings on the fourteen patients with typical acromegaly. In four of these chromophil adenoma was surgically verified. One patient (case 3) had a mixed adenoma and one (case 12), a cystic adenoma, one patient is included in whom the acromegaly was thought to be a part of a polyglandular syndrome. Eight of them received roentgen treatments either supplementary to or in place of, an operation. There are two points to which special attention should be called.

(a) *Specific Dynamic Action* — When expressed as the highest percentage increase over the basal metabolism, this varied from 6.5 to 38.7 per cent, the average rise being 19.0 per cent. Among those whose metabolism was studied for four hours, two showed the highest rise at the end of the first hour, two at the end of the second and three each at the end of the third and fourth hours. All of the patients showed a definite response to the protein meal.

(b) *Basal Metabolism* — It is known that in acromegaly not only is the basal metabolism usually elevated, but it also becomes lowered following either hypophyseal irradiation or operative excision of the pituitary adenoma. The figures in table 1 confirm these points. The



TABLE 1—*Patients with Acromegaly*

Case	Age	Sex	Date	Height, Cm	Weight, Kg	Surface Area Sq M	Metabolism (Percentage from Normal)					Highest Percent Increase Over Basal Metabolism	Comment
							Time After Ingestion of Beefsteak						
							Basal	1 Hour	2 Hours	3 Hours	4 Hours		
1	28	M	10/28/30	169.5	79.7	1.92	+7	+36	+21	+29	+31	27.1	102 Gm of beefsteak, definite acromegaly, small sella
2	29	M	10/23/30 10/27/30	172.0	69.1 68.9	1.81 1.81	—2 —3	+18	+16	+23	+12	26.8	178 Gm of beefsteak, early definite acromegaly
3	46	F	11/6-7/30 12/17-23/30 12/22/30		61.3	1.72	Roentgen treatments +2.5					? Faulty determination	
			8/10/26	157.0	61.9	1.62	+19						Typical acromegaly
			8/12/26		61.0	1.61	+17						Transphenoidal, extirpation of verified adenoma
			8/16/26				Operation						
			9/10/26		58.8	1.59	+9						
			9/23/26		59.2	1.59	+1						
			8/24/27		66.3	1.67	+5						
			8/25/27										
			10/4/27		65.3	1.66	+1						
			10/4-6/27										
			10/7/27		65.3	1.66	—6						
			10/12/27		65.3	1.66	—1						
			12/12-17/27				Roentgen treatments						
			12/13/27		65.1	1.67	+24						
			12/13/27		68.9	1.70	—4						
			4/5/29		68.5	1.70	—15						
			8/12/30				—1	+7	+16	+1	—1	—5	Slight hypocalcemia
													120 Gm of beefsteak
4	36	M	6/23/26 7/2/26 7/12/26 9/25/26 3/22/28	167.0	73.2 68.2 73.8 74.8	1.82 1.76 1.82 1.83	+16 +3 +2 0						Typical acromegaly Transphenoidal partial removal of chromophil adenoma Marked postoperative recession of symptoms
									+9	+24*		24.0	
5	48	F	9/11/30	167.8	77.2	1.87	+5	+5	+13	+18	+25	19.1	Typical marked acromegaly symp- toms stationary, small sella
6	24	F	1/16/29 1/28/29 5/21/29 5/31-6/3/29 6/6/29 11/8/29 11/12-18/29 1/28/30 2/18-21/30 5/21/31	166.0	63.7 64.0 75.1 74.4 69.2 66.4 59.5	1.71 1.72 1.83 1.82 1.76 1.74 1.67	—1 —2 +13 0 0 —6 —5	+16 +25 4 roentgen treatments 0 0 4 roentgen treatments 4 roentgen treatments 4 roentgen treatments	+16 +27 +28 +7 +7 +7 +7	+16 +27 +28 +16 +28 +28 +28	18.4 11.0 28.0	Acromegaly ? surgically unverified Polyglandular syndrome	



average basal metabolism in the seventy-two patients reported on by Davidoff and Cushing<sup>12</sup> was +18.6 per cent. If we take for comparison the basal determinations noted in table 1 prior to operation or irradiation, we find the average for the group to be 11.5 per cent. In seven of nine instances studied there was a definite lowering of the metabolism following operation or roentgen treatment.

2 *"Fugitive" Acromegaly*—There were seven patients (table 2) who have been grouped under the heading of "fugitive" acromegaly.<sup>14</sup> These persons showed evidence of acromegalic changes, but the disease appeared no longer to be in the active stage. They all showed a normal or relatively low metabolism, and in the four patients operated on there was found a mixed type of pituitary adenoma.

(a) *Specific Dynamic Action* Variations in the percentage rise above the basal metabolism in this group ran from 8.8 to 25.1, the average being 17.9 per cent. None of these patients studied for four hours after the beefsteak meal showed the maximum rise at the end of the first hour. Four showed it at the end of the second hour, one at the third and four at the fourth. Observations made on four different occasions with the patient in case 3 show the variation in the degree of rise that may be seen in one person from day to day. In the first test his metabolism rose from +7 to +28, an increase of 19.6 per cent. Three days later the change was from -4 to +24, an increment of 29.2 per cent. Following the administration of thyroid extract, the basal metabolism was +26 and this rose to +48 an hour and a half after the ingestion of beefsteak, or an 18.5 per cent rise in spite of the high basal level. On a subsequent admission three and one-half years later, the metabolism rose from +16 to +34 at the end of the second hour, which is an increase of 15.5 per cent above the basal calories. Mention will be made later on of these variations in the specific dynamic reaction observed in the same person on different occasions.

(b) *Basal Metabolism* If we omit the determinations made on the patient in case 3 during the time that thyroid extract was given, we find the average basal metabolism for this group to be -1.

3 *Chromophobe Adenoma (Hypopituitarism)*—The third and largest group (table 3) includes those with a chromophobe adenoma often associated with more or less marked evidence of pituitary insufficiency (hypopituitarism). There were thirty-two patients studied in this group, and in nearly all instances the tumor was verified at operation.

(a) *Specific Dynamic Action* This varied, rising from 5 to 41.5 per cent above the basal metabolism, with an average of 23.1 per cent. That this average is slightly higher than the average in the two preceding groups is to be explained in part by the lower level of basal metabolism as mentioned previously in methods of tabulation. The

TABLE 2—Patients with "Fugitive" Acromegaly

Case	Age	Sex	Date	Height, Cm	Weight, Kg	Surface Area, Sq M	Metabolism (Percentage from Normal)										Highest Percentage Increase Over Basal Metabolism	Comment
							Basal	Time After Ingestion of Beefsteak				1 Hour	2 Hours	3 Hours	4 Hours			
								1 Hour	2 Hours	3 Hours	4 Hours							
1	38	F	3/19/30	171.5	68.2	1.80	-1,	-2	+1	+9	+8	+1	25.1	Mixed adenoma verified Transfrontal radical extirpation				
2	41	F	12/16/29 12/28/29	153.0	63.0	1.60	-11 Operation	-7	10	13	+1	23.6						
	27	M	2/7/28 2/10/28 2/17/28 2/28/28 2/28-3/7/28 3/1/28 3/7/28 3/13/28 11/6/31 11/7/31 11/21/31 12/5/31 12/12/31	168.0	66.7 66.8 65.0 64.6 63.3 64.6 64.5 61.1 60.1	1.76 1.76 1.71 1.73 1.72 1.72 1.73 1.71 1.70 1.69	Operation -1 Operation +9 Received 2 grains of thyroid 3 times a day +10 +26 +15 +21 +16 Operation +3 +2	+21 +16	+28* +21*	+1	+1	19.6 29.2						
3	33	F	8/24/26 8/28/26 9/9/26 2/7/27 2/11/27 2/23-24/27 4/25/30	166.4	78.5	1.87	-2 Operation -10 -6 -10 2 roentgen treatments -6	+1	+34	+30	+27	18.5	Transfrontal radical extirpation of mixed adenoma					
5	53	M	1/23/30	86	1.96	1.88 1.92	-2 Operation -10 -6	+1	+1	+1	+1	15.5						
6	26	F	6/26/26 7/6/26 7/21/26 7/24/29 7/29/29 7/21/31 7/22/31	154.8 157.0	67.3 56.7	1.61 1.57	-2 Operation -12 +1 -1	+1	+1	+1	+1	18.1 16.3	Transphenoidal, partial extirpa- tion of mixed adenoma					
7	26	F	3/7/30 3/8/30 4/4-8/30	156.7	73.8 73.5	1.74 1.74	+2 +2 Roentgen treatments	+17	+13	+7	+1	12.5 16.1 8.8 10.8		Transphenoidal radical extirpa- tion of mixed adenoma				
Average												17.9						

\* Metabolism after one and one half hours

\* Metabolism after one and one half hours

TABLE 3—*Patients with Chromophobe Adenoma*

Case	Age	Sex	Date	Height, Cm	Weight, Kg	Surface Area, Sq M	Metabolism (Percentage from Normal)					Highest Percentage Increase Over Basal Metabolism	Comment
							Basal	Time After Ingestion of Beefsteak					
								1 Hour	2 Hours	3 Hours	4 Hours		
1	56	M	1/15/30 1/23/30	171.8	83.2	1.97	Operation -30	-16	-23	-15	-1	41.5	Transfrontal, extirpation of chromophobe adenoma
2	52	F	1/4/30	161.2	97.5 97.7	1.92 1.92	-21	-13	-7	+1	+10	39.2	Same as in case 1
			1/8/30				-13	-7	-3	+1	+5	20.7	
			1/18/30				Operation						
			12/8/30				-13						
			12/10/30				-18						
			12/17/30				-19						
3	51	M	4/17/30 4/18/30	182.0	78.0	1.99	Operation -24	-6	-8	+4	-5	36.8	Same as in case 1
4	51	F	4/16/30 4/23/30	167.0	65.0	1.73	Operation -23	+2	0	+5	+5	36.4	Same as in case 1
5	50	M	6/4/30 6/17/30 6/27/30	178.0	93.6	2.12	Operation -17 Operation -14	-6	+13	-2	-3	36.2	Same as in case 1
6	42	M	9/17/30 9/25/30 10/4/30 10/17/30	164.8	81.6 79.7 81.6	1.89 1.87 1.89	Operation -22 -11 -22	-10	+3	+5	-6	34.6	Same as in case 1
7	34	M	2/12/30 2/24/30	173.0	63.2	1.75	Operation -31	-28	-15	-18	-10	30.4	Same as in case 1
8	44	F	6/21/28 6/27/28 7/5/28 7/11/28 7/23/28	167.5	59.8 61.2 59.0 59.0	1.68 1.69 1.67	Operation -12 -16 -19 -25						Same as in case 1
9	22	M	6/21/30	179.0	74.5	1.94	Operation -22	-7	-1	-7	-6	26.9	Chromophobe adenoma unverified
10	35	F	10/11/28 10/24/28	154.7	55.3	1.53	Operation -24	-4	-8			28.4 20.0	Extirpation of chromophobe adenocarcinoma
11	23	M	2/14/25 2/27/25 4/18/25 2/15/29 2/25/29	162.5	66.7 69.3 72.3 70.3	1.72 1.74 1.78 1.75	Operation -33 -28 -25 -27					26.3	Transphenoidal, extirpation of chromophobe adenoma
								-19	-8			26.0	

12	42	M	7/16/30 7/21/30	172.7	73.9	1.88	-15 Operation	+7	-4	-1	+6	25.9	Transfrontal, extirpation of chromophobe adenoma
13	42	M	1/3/30 1/15/30	165.6	83.6	1.91	-10 Operation	-2	+5	+8	+11	23.4	Same as in case 12
14	42	F	3/21/30 5/23/30 6/21/30 6/26/30	170.0	75.3 75.3 75.3 66.5	1.86 1.86 1.86 1.68	-18 Operation -25 -20 -16 Operation	-15	-9	-2	+1	23.1	Same as in case 12
15	25	F	8/25/27 8/30/27 9/13/27 1/16/29	137.5	63.4 67.1	1.67 1.69	-20 -21 -9 -10 Operation	-9	-3			22.8	Same as in case 12
16	39	M	6/6/28 6/19/28 6/22/28 7/5/28 7/6/28	163.0	66.5 68.0 64.4 61.9	1.72 1.73 1.70 1.71	-9 -10 Operation -16 -2	-3	+10			22.2	Same as in case 12
17	36	M	8/2/29 8/7/29 9/6/29 2/21/30 2/27/30 6/16/31	174.4	73.5 69.4 63.8 65.0 70.3	1.89 1.83 1.77 1.78 1.81	-26 Operation -44 -31 -37 -33	+15	0			11.7	? Faulty observation
18	50	F	7/21/30 8/19/30	159.5	58.6	1.60	-9 Operation	+2	-7	+5	+11	22.0	Same as in case 12
19	29	F	10/10/29 10/23/29	153.6	49.6	1.45	-16 Operation	-10	0	+2	-8	21.4	Same as in case 12
20	26	M	1/13/30 1/23/30	171.6	72.7	1.85	-24 Operation	-20	-8	-12	-13	21.0	Same as in case 12
21	51	F	1/2/29 1/18/29 2/8/29 2/15/29	178.0	56.2 53.0 54.1	1.71 1.61 1.63	-16 Operation -27 -28		-13			20.8	Same as in case 12
22	23	F	2/24/30 3/5/30 3/6/30 4/8/30	151.2	51.3 51.7	1.46 1.46	-21 -25 Operation -22	-13 -18	-3 -8	-10 -8	-5 -2	20.1 30.6	Same as in case 12
23	22	M	12/5/29 12/9/29	164.2	48.5 54.4	1.41 1.58	-20 Operation	-8	-15	-8	-4	20.0	Same as in case 12
24	67	M	5/10/30 5/19/30 6/9/30 6/11/30	175.2	68.2 62.0 59.6	1.83 1.76 1.73	-8 Operation -22 -24	-5	+7	-2	+9	18.5	Same as in case 12

\* Metabolism after one and one half hours

TABLE 3—Patients with Chromophobe Adenoma—Continued

Case	Age	Sex	Date	Height, Cm	Weight, Kg	Surface Area, Sq M	Metabolism (Percentage from Normal)					Comment
							Time After Ingestion of Beefsteak				Highest Percentage Increase Over Basal Metabolism	
							Basal	1 Hour	2 Hours	3 Hours		
25	44	M	10/28/26	176.8	83.8	2.01	Operation +21					Transphenoidal, chromophobe adenoma, possibly of mixed type 146 Gm of beefsteak Transfrontal, recurrence of adenoma of same type
			11/5/26				Operation —5					
			11/26/26	175.6	73.8	1.90	0					
			9/20/30		90.3	2.07	Operation —12					
			9/22/30		86.7	2.04	—10					
26	66	F	10/3/30		89.0	2.06	—10					Transfrontal extirpation of chromophobe adenoma
			10/7/30				—10					
			5/19/30	166.0	49.4	1.53	Operation —10	—11	—3	+1	+1	
			5/24/30				Operation —26					
			6/19/30		50.1	1.51						
27	39	F	8/7/30	160.0	87.7	1.91	+2					110 Gm of beefsteak Radical removal of cystic adeno carcinoma
			8/9/30		87.7	1.91	+4					
			8/12/30				Operation	+15	+17	+20	+19	
			7/5/28	182.0	74.2	1.95	—26					
			7/7/28		73.3	1.94	—22					
28	50	M	7/11/28				Operation	—18	—10			Transfrontal, extirpation of chromophobe adenoma
			7/25/28		72.6	1.93	—28					
			1/5/32		75.0	1.95	—25					
			1/6/32		75.0	1.95	—30	—23	—25	—23	—17	
			7/21/28	165.0	63.5	1.70	—7					
29	18	M	7/23/28		63.5	1.70	—16					Same as in case 28
			8/1/28				Operation					
			8/11/28		56.8	1.63	—19					
			8/15/28		59.1	1.65	—20					
					87.3	1.88	—11	—11	—8	—2	—2	
30	45	F	2/20/30				Operation					150 Gm of beefsteak Same as in case 28
			3/1/30				—8					
			3/18/30		80.5	1.81	—5					
			3/29/30		79.1	1.79	—5					
					83.8	1.72	—23					
31	37	M	9/24/27	160.2	83.6	1.72	—12					Same as in case 28
			10/1/27				Operation					
			10/4/27				—10					
			10/18/27		67.1	1.70	—5					
			10/20/27		66.9	1.70	—6					
32	30	M	4/20/28		66.5	1.69	—6	+3	+5*			100 Gm of beefsteak Marked hypopituitarism Chromophobe adenoma with hem orrhagic cyst, partial extirpation
			11/26/28	169.0	57.0	1.65	—36					
			12/4/28		53.9	1.61	Operation					
			12/31/28		54.3	1.61	—26					
			1/4/29				—30	—24	—21*			
Average							—19					5.0 23.1

\* Metabolism after one and one half hours

time of the "peak" of metabolism increase in this group is of interest because it occurs in most instances late in the period of observation. Of twenty-five patients studied for four hours after the meal, only one showed a peak at the end of the first hour, five at the end of the second hour, seven at the third and twelve at the fourth. Further comments on this point will be made later in the discussion. It is in this group of patients with diminished pituitary function that one should find a lessened response to the stimulation of a protein meal if the contention is true that the hypophysis influences the specific dynamic action of food. Not only was there a definite increase in the metabolism in each instance in this group, but the average increase was higher than any of the other groups of patients with pituitary disorders.

(b) Basal Metabolism. As previously pointed out,<sup>1</sup> the basal metabolism in patients with this type of pituitary adenoma is usually at a low level. With only four exceptions, all of the eighty-three determinations of the basal metabolism were below zero, and sixty-four (77.1 per cent) of them were less than  $-10$ . The average for the entire group was  $-19$ .

4 *Patients with Parahypophyseal Tumors*—There were sixteen patients studied (table 4) in whom many features suggested, early in their course, a disturbance of pituitary origin. These were found later either at operation or by further clinical study to have, not a primary pituitary disorder, but a lesion in the region of the hypophysis producing secondarily the picture of pituitary insufficiency. In many respects, then, they were similar to the preceding group with chromophobe adenomas. There were five with tumor of the third ventricle, three with craniopharyngioma, two with suprasellar meningioma, two with suprasellar cyst, one with a willisian aneurysm, and three in which an anatomic diagnosis was not made.

(a) Specific Dynamic Action. Variations in the percentage rise in this group ran from 9.6 to 35.5, the average being 20.4. Two showed the maximum rise at the end of the first hour, one each at the end of the second and third and eight at the end of the fourth.

(b) Basal Metabolism. As in the group with chromophobe adenomas, the basal metabolism was distinctly lowered, the average being  $-17$  with twenty-five of thirty-seven determinations (67 per cent) registering below  $-10$ .

5 *Control Group*—The test was carried out on thirteen patients (table 5) who were shown subsequently not to have a pituitary tumor or any definite lesion in the vicinity of the hypophysis. This group serves as a control on the others. In the column of "comment" one may see the wide variety of conditions represented among these thirteen patients.



TABLE 4—*Patients with Parahypophyseal Tumors*

Case	Age	Sex	Date	Height, Cm	Weight, Kg	Surface Area, Sq M	Metabolism (Percentage from Normal)					Highest Percentage Increase Over Basal Metabolism	Comment
							Basal	Time After Ingestion of Beefsteak					
								1 Hour	2 Hours	3 Hours	4 Hours		
1	50	F	10/ 9/29	153.6	52.9	1.49	-24	-6	-1	-2	+3	35.5	Hypertension, willisian aneurysm unverified
2	41	M	4/14/30	171.0	83.1	1.95	-10	-4	+11	+13	+17	45	Hypertension, adiposity, bitemporal hemianopia
3	48	F	8/23/28 8/25/28 9/21/28	162.6	59.9 59.0	1.64 1.63	-14 -15 Operation	+13	+14			0	Suprasellar meningioma
4	24	M	4/14/26 7/12/26 3/16/27 3/22/30	167.5	55.5 56.7 57.9 63.7	1.63 1.65 1.65 1.70	-26 -28 -30 -28	-11	-8	-15	-7	29.2	Cranio-pharyngioma verified
5	16	F	1/11/26 2/26/30 3/ 7/30 4/16/30	138.0 156.8	27.2 52.0	1.04 1.50	-16 -11 Operation	+2	-1	+4	+10	26.4	Transventricular, extirpation of astroblastoma of third ventricle
6	46	M	10/ 5/28 10/10/28 11/ 5/28	177.6	86.0 86.0	2.03 2.03	-32 -27 Operation	-10	-10			23.3	Transfrontal, craniopharyngioma verified
7	25	M	7/20/29 7/23/29	136.5	31.2 31.7	1.09 1.10	-20 -12	+3	+8			22.8	Pituitary dwarfism (Simon's)
8	10	F	2/23/28 2/24/28 5/29/28 6/ 1/28 6/25/28 7/ 6/28	138.5 139.5	40.1 40.3 41.7 41.3	1.23 1.23 1.25 1.25	-32 -20 -23 -27 Operation	-14 +5 -19 -30	-17* -2* -19* -32			21.2 36.4 10.9 22.8	Cranio-pharyngioma Transfrontal, evacuation and partial removal of cyst



TABLE 5—Control Group of Patients

Case	Age	Sex	Date	Height, Cm	Weight, Kg	Surface Area, Sq M	Metabolism (Percentage from Normal)						Highest Percentage Increase Over Basal Metabolism	Comment
							Basal	Time After Ingestion of Beefsteak						
								1 Hour	2 Hours	3 Hours	4 Hours			
1	53	M	5/17/30 5/22/30	160.3	61.0	1.68	-34 Operation	-18	+ 2	-15	- 7	54.5	140 Gm of beefsteak. Occipital glioma; verified	
2	9	F	2/28/28 3/ 2/28	133.4	27.5 27.1	1.01 1.00	-29 -20	+ 6	+ 5			32.5	Cerebral tumor unverified	
3	33	F	11/ 1/26 12/24/28 11/30/29	171.0	76.0 80.5 81.9	1.88 1.93 1.94	-10 -10 -15	-14	0	0	+10	29.4	Obscure polyglandular disorder	
4	13	F	2/13/30	154.5	57.4	1.55	-18	- 2	+ 1	+ 2	+ 4	26.8	165 Gm of beefsteak, angiomas of retinas	
5	60	F	2/19/30	154.0	59.3	1.57	- 1	+16	+23	+23	+17	21.2	120 Gm of beefsteak, osteitis deformans	
6	28	F	6/ 5/30	163.1	62.3	1.71	-17	- 1	- 3	+ 3	- 3	24.1	Hydrocephalus, cerebral tumor unverified	
7	47	M	9/ 4/30		67.9	1.77	-18	+ 3	+ 1	0	+10	34.2	120 Gm of beefsteak	
8	37	M	12/ 9/29	176.0	105.1	2.21	-12	+ 3	+ 1	+ 6	+ 3	20.4	Vasomotor instability	
9	30	M	12/11/29	171.0	132.5	2.98	+18	+33	+37	+39	+36	17.8	Intracranial tumor unverified	
10	39	F	8/13/30 2/ 3/31 2/ 9/31 10/28/31 10/31/31	184.2 150.5	86.8 55.8	2.10 1.51	-10 + 3 Operation	- 1	- 1	0	+ 4	15.5	Obscure endocrinopathy, adiposity with glycosuria	
					59.4 59.4	1.54 1.54	- 3 - 5	+12	+ 3	+18	+16	14.5	146 Gm of beefsteak Meningioma	
11	30	M	12/14/29 12/19/29	179.6 164.2	64.0 64.2	1.81 1.81	- 4 -10	+15	+19	+26	+24	32.6		
12	13	F	10/25/29	180.4	67.2	1.85	-19	- 5	- 7	0	- 2	11.1	Chronic meningitis	
13	15	F	5/ 3/28 5/10/28 6/28/28 6/30/28	178.0 198.0 197.3 196.1 196.5	98.0 97.3 95.1 95.5	1.99 1.97 1.96 1.96	+ 1 - 6 - 1 - 6	-10	-21	-16	-15	11.1	Obscure endocrinopathy	
								- 4	- 4			2.1	Adipositas cerebriilis?	
Average							-10					23.4		

(a) Specific Dynamic Action The average percentage increase here was 23.4, with 2.1 and 54.5 as extremes. This is the highest average rise of any of the groups, though it differs by only 0.3 per cent from that found in patients with chromophobe adenomas, and is to an extent influenced by the low average basal metabolism of  $-10$ . The peak of metabolism increase was again found to occur more commonly after the third or fourth hour, ten of the four hour tests showing the highest rise at this time as compared with two after the second hour and one after the first.

(b) Basal Metabolism There is little of note concerning this, excepting the extremes of  $-34$  and  $+18$ , with  $-10$  as the average for the group.

## COMMENT

This study is reported to show the effect of a protein meal on the metabolism of patients with pituitary disease. In the foregoing statements of results the essential facts are presented. They may be sum-

TABLE 6—*Effect of Protein Meal on Metabolism in Pituitary Disease*

Group		Number of Patients	Average Basal Metabolism	Average Highest Percentage Increase in Metabolism after Beefsteak Meal
I	Acromegaly	14	+11.5	19.0
II	Fugitive acromegaly	7	$-1.0$	17.9
III	Hypopituitarism	32	$-19.0$	23.1
IV	Parahypophyseal tumor	16	$-17.0$	20.4
V	Control	13	$-10.0$	23.4
Average				20.7

marized briefly in table 6. These figures show that in patients with pituitary disorders there is an increased heat production of essentially the same magnitude as that found in normal persons by other workers.<sup>17</sup> In other words, a disturbance of pituitary function, whether due to either of the usual types of pituitary adenomas or to pressure on the hypophysis from an adjacent tumor, does not have any influence one way or the other on the metabolic response to a protein meal. The large mass of data presented here affords at least that answer to the question: Does the pituitary gland have any direct bearing on the specific dynamic action of food?

There are one or two further points in this study to which attention may be called. The first is the variation in the degree of rise in metabolism after food that may be seen in the same person from day to day. Whereas, in some instances this is found to be relatively constant (as

<sup>17</sup> Wang, C. C., Strause, S., and Saunders, A. D. Studies on the Metabolism of Obesity. III. The Specific Dynamic Action of Food, *Arch. Int. Med.* **34**: 573 (Oct.) 1924. Strang and McClugage.<sup>15</sup>

in cases 6 and 7, table 2, and cases 10 and 15, table 4), in others there is considerable difference in the extent of the rise on repeated tests. The following are examples of this among the persons on whom more than one four hour test was carried out (table 7)

In part, these differences in the percentage increase of metabolism are due to differences in the basal metabolism on the two days which give an artificial magnification to the increased heat production. Strang and McClugage found a similar variation in the response to food in some of their well trained patients who had repeated tests. It is entirely probable that the total heat production in our patients measured

TABLE 7—*Data on Patients Given More Than One Four Hour Test*

Patient	Date	Basal Metabolism	Percentage Increase after Beefsteak Meal
Case 13 (table 1)	12/ 9/30	+13	14.2
	1/ 2/31	— 7	38.7
Case 2 (table 3)	1/ 4/30	—21	39.2
	1/ 8/30	—13	20.7
Case 22 (table 3)	2/24/30	—21	20.1
	3/ 5/30	—25	30.6
Case 6 (table 5)	6/ 5/30	—17	24.1
	9/ 4/30	—18	34.2
Case 10 (table 5)	2/ 3/31	+ 3	14.5
	10/31/31	— 5	32.6

TABLE 8—*Peak of Metabolism Rise at Different Intervals*

Group	1 Hour	2 Hours	3 Hours	4 Hours
I Acromegaly	2	2	3	3
II Fugitive acromegaly	0	4	1	4
III Hypopituitarism	1	5	7	12
IV Parahypophyseal tumor	2	1	1	8
V Control	1	2	6	4
Total	6	14	18	31

over a period of eight hours would not show any such variation as is suggested by the change in percentage increase of metabolism on different days. It has been shown by several observers<sup>18</sup> that there is no appreciable difference in the total heat effect of a meal as observed when repeated tests are done on the same person.

A second point is the time of the "peak" of metabolism rise in this series of patients. This has been noted previously for each group. In summary, the figures are as shown in table 8.

In the sixty-nine four hour tests carried out, we find the highest metabolism at the end of three or four hours in forty-nine, or 71 per

<sup>18</sup> Lauter, S. Zur Genese der Fettsucht, *Deutsches Arch f klin Med* **150** 315 (March) 1926. Strang and McClugage<sup>15</sup>

cent This is in keeping with the studies reported by others,<sup>19</sup> which show that after a meal consisting mainly of protein, the highest metabolism is most commonly found during the third and fourth hours Strang and McClugage found the maximum response at an earlier time, but their test meal contained considerable carbohydrate which would have a more prompt effect on the metabolism As they point out, the palatability of the food and its psychic effect on gastric secretion, the rate of emptying of the stomach and absorption of the digestion products from the intestine will all influence the speed of the metabolic response

#### CONCLUSIONS

The specific dynamic action of protein was observed in fifty-three patients with pituitary disease, sixteen others with parhypophyseal tumors and thirteen control subjects The metabolic response to the protein meal was essentially the same in all the groups and was well within the range of normal limits

The study indicates that disturbance in pituitary function as seen in man has no influence on the specific dynamic action of protein It lends further support to the view that the endocrine glands have no direct bearing on the specific dynamic action of food

Miss Kathryn Weitzel and Miss Maude Lacey rendered technical assistance

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<sup>19</sup> Gephart, F C, and Du Bois, E F Clinical Calorimetry IV The Determination of the Basal Metabolism of Normal Men and the Effect of Food, *Arch Int Med* **15** 835 (May) 1915 Mason, E H, Hill, E, and Charlton, D Abnormal Specific Dynamic Action of Protein, Glucose, and Fat Associated with Undernutrition, *J Clin Investigation* **4**:353 (Aug) 1927 Aub and Means<sup>7</sup>

# EFFECT OF DIGITALIS ON THE CORONARY FLOW

N C GILBERT, M D

AND

G K FENN, M D

CHICAGO

The effect of digitalis on the coronary vessels or on the volume of coronary flow has received a very moderate amount of attention. The clinical and experimental evidence for or against any change in coronary flow with the administration of digitalis has been conflicting and not altogether convincing.

Clinical observation of the effect of digitalis cannot be adequately controlled, and there is always the possibility that a favorable or untoward result following the administration of digitalis might equally have ensued if the drug had not been given. When the effect of digitalis on auricular fibrillation, on minute volume output or on edema is considered, one has measurable results to record. This is not possible in the case of the effect of digitalis on coronary flow.

Our own clinical experience led us to believe that untoward effects might occur with the use of digitalis in coronary disease, and that these effects might be due to coronary vasoconstriction.

Experimental work has previously been done to ascertain the effect of digitalis on arterial strips, on the isolated heart and on preparations of the intact animal. Cow,<sup>1</sup> using arterial strips, found evidence of vasodilatation of the coronary artery when watery solutions of digitalis were added to the solution in which the artery strip was suspended. Strips of other arteries contracted under the same conditions. Voegtlin and Macht,<sup>2</sup> Eppinger and Hess,<sup>3</sup> Rabe<sup>4</sup> and others have shown a contraction of arterial strips from the coronary. Rabe<sup>4</sup> showed that strophanthin constricted the coronaries in a dilution of 1:20,000,000, while a dilution of 1:1,000 showed either no effect or only a slight effect on peripheral vessels. Digitalin constricted the coronary arteries in a 1:5,000,000 dilution, but constriction of the peripheral vessels

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1 Cow. *J. Physiol.* **42** 125, 1911.

2 Voegtlin and Macht. *J. Pharmacol. & Exper. Therap.* **77** 5, 1913.

3 Eppinger and Hess. *Ztschr. f. exper. Path. u. Therap.* **5** 622, 1908.

4 Rabe. *Ztschr. f. exper. Path. u. Therap.* **11** 175, 1912.

occurred only in a 1:10,000 dilution. The results of experiments by the same author on the effect of other drugs on arterial strips agree with other experimental and clinical observations, and, in spite of certain objections to the method, we feel that the results are significant.

The results obtained by various workers on the isolated heart show preponderantly that there is a vasoconstrictor action on the coronary arteries by digitalis. Cushny<sup>5</sup> objected to drawing any conclusions from results obtained on the isolated heart because of the frequent changes in the activity of the heart during the experiment, and also because of the use by the investigators of concentrations of the drug in excess of those that would be administered clinically. Meyer<sup>6</sup> stated that in the isolated heart there is only a short second stage during which pharmacologic experiments are of any value.

Our own unpublished experiments with this method would tend to confirm the objections of Cushny and of Meyer. By perfusion with oxygenated Locke's or Ringer's solution, we obtained striking evidence of coronary vasoconstriction with concentrations of the drug comparable to or less than those used therapeutically.

When oxygenated heparinized whole blood was used as a perfusing solution, similar small doses failed to give conclusive results. In addition, an empty beating heart allowed to beat for long periods under constant conditions without any experimental interference shows so many spontaneous variations as to render doubtful any results obtained with drugs.

Bodo,<sup>7</sup> using the heart-lung preparation, in which venous inflow, pulse rate, peripheral resistance and blood pressure were controlled and constant, found a small increase in the coronary flow with digitalis. It is possible that the simultaneous use of a Henderson cardiometer influenced the results, as changes in tonus would alter the pressure of the cardiometer diaphragm.

There have been comparatively few experiments on the intact animal. Bond<sup>8</sup> suspended a cat face downward with the apex of the heart held in position by a suture. A cut was made in a coronary vein, and the drops were counted as they fell. He found no change in flow to result from digitalis administration. Meyer,<sup>6</sup> in curarized cats, passed a cannula into a superficial vein and measured the flow. He found an increase in flow with digitalis bodies. It is possible that the effect of the curare on the sympathetic ganglion may have influenced his results.

5 Cushny, Arthur. *Digitalis and Its Allies*, New York, Longmans, Green & Co., 1925.

6 Meyer, F. *Arch f. Physiol.*, 1912, p. 223.

7 Bodo, R. *J. Physiol.* **64**: 365, 1928.

8 Bond. *J. Exper. Med.* **12**: 575, 1910.



Sakai and Saneyoshi<sup>9</sup> performed their experiments on the intact animal, using cats under ethyl carbamate (urethane) anesthesia. A Morovitz cannula was passed through the auricular appendage into the coronary sinus, and the flow was measured. They found a vasoconstrictor effect from large doses of strophanthin, but with doses approximating those used clinically the coronary flow followed the blood pressure without evidence of vasoconstriction or of vasodilatation.

#### METHOD

We conducted our own experiments on the intact animal with a preparation very similar to that of Sakai and Saneyoshi. A short experience with the use of single doses of varying size convinced us that results obtained by this method are of small value. In the intact animal, even with conditions such as venous return, temperature, etc., kept constant, there still remain variations in pulse and blood pressure that vitiate the results from the administration of single doses. To attempt to obviate these difficulties we decided to use a large number of dogs, and to make first a control series of experiments in which the variations in coronary flow under standard conditions were observed over a period of from one and a half to two hours without the use of any medication. Similar series of tests were then made under identical conditions, but with fractions of the estimated lethal dose of digitalis administered at regular intervals until death. A comparison of the results in the control series and in the series in which digitalis was administered should throw some light on the effect of digitalis on the coronary flow.

The anesthetics used were diallylbarbituric acid, sodium barbital, chlorbutanol and the Grehanst anesthetic (5 per cent chloroform in a solution of equal parts of alcohol and water). We could detect no difference in the effect of these.

The technic was the same as that previously reported by us<sup>10</sup>. The chest was opened in the midline and a modified Morovitz cannula passed through the right auricular appendage into the coronary sinus. The cannula was connected with the cylinder of a piston recorder, and the rise of fluid level in the cylinder traced on a revolving drum. With a known capacity of the cylinder of the piston recorder, the volume of the coronary flow was readily estimated by measurement of the rise of the line traced on the drum.

The blood was returned to a jacketed cylinder kept at a constant temperature and connected with the femoral vein. The height of the cylinder was adjusted so as to admit of a volume of return flow approximately equal to the volume flowing out through the coronary cannula. The pressure remained constant throughout the experiment, and was not changed to meet variations in venous pressure. The fluid level in the return flow cylinder was kept constant by a simple device that functioned automatically. The temperature of the animal and that of the return flow were constant for the experiment.

Blood pressure was recorded from the carotid artery by a mercury manometer. The experiment was not started until the preparation had become stabilized, the return flow was adjusted to meet the volume of blood flow from the coronary sinus, and blood pressure and pulse rate were at an almost constant level.

<sup>9</sup> Sakai and Saneyoshi. *Arch exper Path u Pharmacol* **78** 331, 1914.

<sup>10</sup> Gilbert, N. C., and Fenn, G. K. The Effect of the Purine Base Diuretics on the Coronary Flow, *Arch Int Med* **44** 118 (July) 1929.

Such an experiment establishes obviously abnormal conditions, but comes as close to normal conditions as any method that we know of for measuring coronary flow. The trauma of the operation and that of the cannula in the sinus offer many variables, but they are constant for the experiment. During the experiment there is a progressive shift of the hydrogen ion concentration of the blood toward the acid side, but this and any increase in metabolites would tend to increase rather than to diminish the coronary flow. Whatever the variables may be, they prevail equally in the control series. Concerning the anesthetic, it may be asked whether such a traumatized animal under full anesthesia offers more variables in the way of vasodilator and vasoconstrictor reflexes than a conscious, normal animal in which the reflex pathways to the coronary arteries are open to stimuli from a multitude of sources.

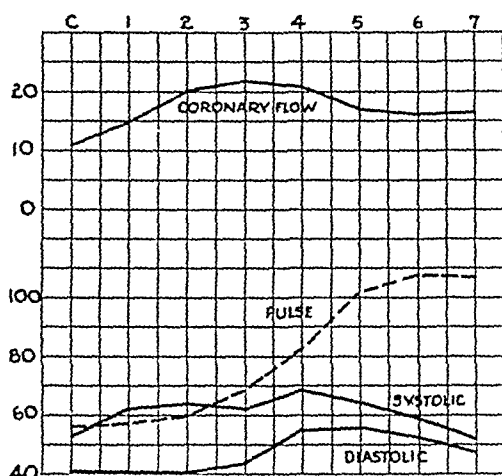


Chart 1—Results of a single experiment on a control animal (dog 46), in which the course of the coronary flow, systolic and diastolic pressure and pulse rate were observed and recorded over a period of time comparable to that in the experiments in which digitalis was used. In this and in all subsequent charts the abscissas represent fluctuations in coronary flow, blood pressure and pulse rate. The ordinates indicate the control reading, represented by (C) and the subsequent readings at ten minute intervals. The upper curve represents the coronary flow in cubic centimeters per minute, charted at ten minute intervals. Readings of the blood pressure in millimeters of mercury, and of the pulse rate in beats per minute, are charted at the corresponding intervals.

The fact that blood pressure was not controlled would have rendered the whole series, even with the control experiments, of much less value had it not been that there was a certain proportion of cases in which digitalis was used and in which the coronary flow decreased with digitalis in spite of an increase in systolic and diastolic pressure and in pulse rate. It is only such cases in which we have assumed that digitalis exerted a vasoconstrictor action. It is quite possible, but not proved, that there was a vasoconstrictor action in at least part of the cases in which either blood pressure or pulse rate decreased.

## CONTROL SERIES

The coronary flow was measured over a period of from one and one-half to two hours under the same standard conditions in which the effect of digitalis was observed. Ten dogs were used, and at the conclusion of the experiments with digitalis three more were added in order to determine whether the results conformed to those obtained earlier. The results of a typical control series are plotted in charts 1 and 2. The volume of coronary flow in cubic centimeters per minute, the systolic and diastolic pressure in millimeters of mercury and the pulse rate at ten minute intervals are plotted. In chart 1, the coronary flow is shown to rise with the blood pressure and pulse rate for the first ten minutes. In the next ten minutes the coronary flow continues

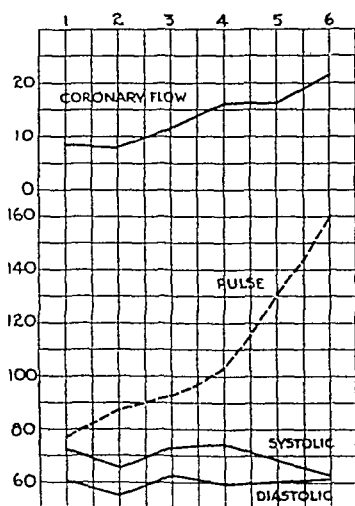


Chart 2—Results of a second control experiment (dog 48), in which the coronary flow and its determining factors follow a somewhat different course

to rise, with a falling systolic and an almost level diastolic pressure, but with a rising pulse rate. In chart 2 is also seen evidence of the effect of the pulse rate on the coronary flow. Smith<sup>11</sup> has reviewed the effect of the pulse rate on the volume of coronary flow and has given the results of his own work on the isolated heart. He expressed the belief that reduction and acceleration of the cardiac rate within certain limits are associated with definite changes in the rate of coronary flow. Our experience in this work confirms this, and we feel that the pulse rate must be considered as a factor in the volume of coronary flow.

<sup>11</sup> Smith, F. M. The Coronary Circulation, *Arch Int Med* 40:281 (Sept) 1927

The results of the control series are summarized as follows

	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	0
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	2
Increase in coronary flow accounted for by rise in blood pressure or pulse rate	11

It will be observed that there was no decrease in coronary flow that could not be accounted for by a fall in systolic or diastolic pressure or pulse rate, and that the volume of coronary flow followed changes in these factors. If we assume that the volume of coronary flow is a function of diastolic and systolic pressure only, disregarding the effect of the pulse rate, the results are as follows

	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure	1
Decrease in coronary flow accounted for by fall in blood pressure	1
Increase in coronary flow accounted for by rise in blood pressure	7
Increase in coronary flow unaccounted for by rise in blood pressure	4

Here there appears a decrease in coronary flow that is not accounted for by a fall in blood pressure, but there also appear four cases in which there was an increase in coronary flow without an underlying rise in blood pressure

#### EFFECT OF DIGITALIS

In a series of twenty-five dogs under identical conditions, one tenth of the estimated lethal dose of a standardized market preparation of the whole leaf of digitalis was given every ten minutes, and in some experiments every seven minutes, until the lethal dose was reached. The preparation used was purchased on the market and was found to be accurately standardized in cat units. One and one-quarter cat units per kilogram was considered as the lethal dose. In the light of our experience we consider this dosage too high. One cat unit per kilogram represents more closely the proper dosage. This preparation will be referred to as whole leaf preparation 1. The series used was large, but we do not consider it to be any too large when important conclusions are to be drawn from animal experiments in which many variations are inherent.

Chart 3 shows the results of such an experiment. The control reading is designated by (C), and one tenth of the calculated lethal dose was given directly after the control reading and directly after each of the readings represented by the subsequent numerals. Thus the reading at (1) shows the results of the injection of the first fraction, the reading at (2) the results of the dose given directly after the readings were taken at (1), and so on. In this experiment the coronary

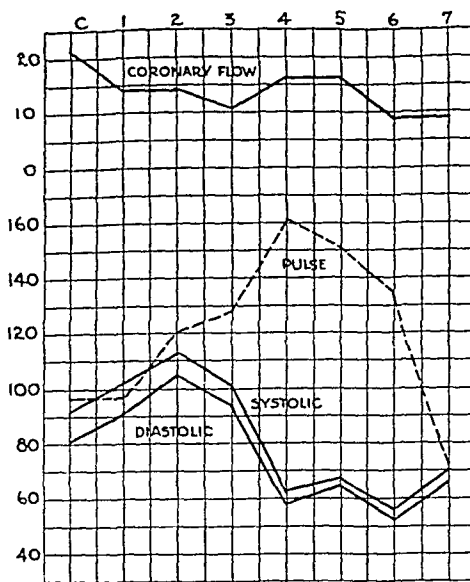


Chart 3—In this experiment one tenth of the estimated lethal dose of digitalis (whole leaf preparation 1) was given every ten minutes to dog 58. At (C) are plotted the coronary flow volume in cubic centimeters per minute, the pulse rate and the systolic and diastolic blood pressure of the last control reading. One tenth of the estimated lethal dose of digitalis was given immediately after (C). At (1) are shown the coronary flow volume, blood pressure and pulse rate ten minutes later. A second tenth of the estimated lethal dose was given immediately after (1), and the results are shown at (2), and so on. The volume of coronary flow is seen to decrease after the first dose, in spite of an increase in blood pressure and in pulse rate.

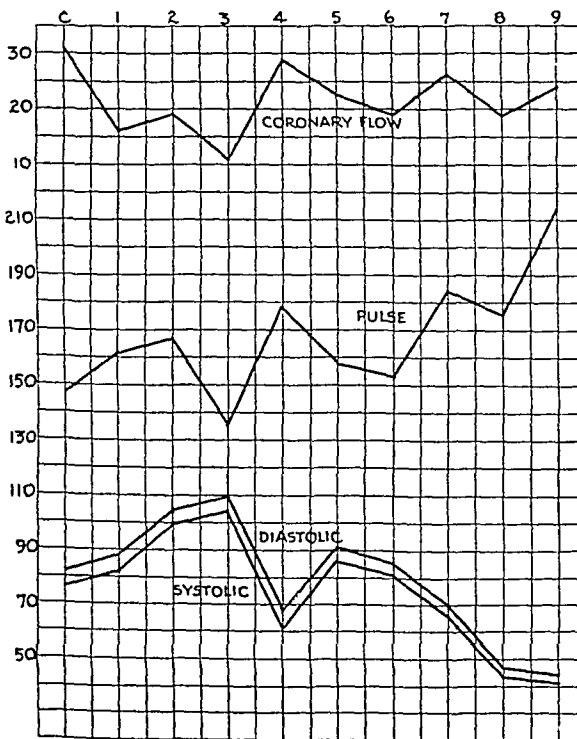


Chart 4—The results of another experiment (on dog 66) similarly plotted to show the effect of pulse rate on volume of coronary flow, and the decrease in volume of coronary flow with digitalis (whole leaf preparation 1) in spite of an increase in blood pressure and in pulse rate following its administration.

flow is observed to decrease with a rising blood pressure and a rising pulse rate. This chart shows the type of result that we considered to indicate a vasoconstrictor action, and that we shall later classify as "decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate." Chart 4 is shown also in order to illustrate the effect of the pulse rate on the coronary flow volume. The variations in coronary flow in this experiment closely follow the variations in blood pressure, but the fall in blood pressure probably offsets an increase in coronary flow corresponding to the rise in pulse rate. In some cases the coronary flow seems to be more a function of the blood pressure and in other cases more a function of the pulse rate, but usually more or less a resultant of the two.

We have inserted chart 5 to show the type of result that we do not feel justified in accepting as an indication of a vasoconstrictor action, although such an action may have been present. The fall in blood pressure and coronary flow at the second control was caused by a kink in the venous return flow tube. When the digitalis was injected after the fourth control reading, there was a small decrease in coronary flow, but there were also a slight decrease in blood pressure and a marked decrease in pulse rate. It illustrates the type that we have later classified as "decrease in coronary flow accounted for by change in blood pressure or pulse rate." We consider that a vasoconstrictor action could be easily read into this tracing, but it does not admit of proof, and we have not used this or similar results as indicating a vasoconstrictor action.

After from 20 to 30 per cent of the calculated lethal dose has been administered, so many variables appear, owing to the action of digitalis on other cardiac functions that we do not consider that any accurate deductions can be made in regard to the effect of digitalis on the coronary flow. It is probable that most of the digitalis used therapeutically is within these limits.

The results of the experiment with the whole leaf preparation 1 may be summarized as follows:

	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	12
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	9
Increase in coronary flow accounted for by increase in blood pressure or pulse rate	4

Twelve dogs showed a decrease in coronary flow that could not be accounted for by a fall in blood pressure or pulse rate. In the remainder of the experiments a rise or a fall in the volume of coronary flow followed a rise or a fall in blood pressure or pulse rate. If the

volume of coronary flow is taken as a function of blood pressure alone, the results with whole leaf preparation 1 are as follows (variations in pulse rate disregarded)

	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure	14
Decrease in coronary flow accounted for by fall in blood pressure	7
Increase in coronary flow accounted for by rise in blood pressure	3
Increase in coronary flow unaccounted for by rise in blood pressure	1

According to these results fourteen dogs showed a decrease in coronary flow without a fall in pressure, and in most cases with a rise in pressure. One animal showed an increase in coronary flow without a corresponding increase in pressure, but in the control series similarly considered four dogs showed such an increase.

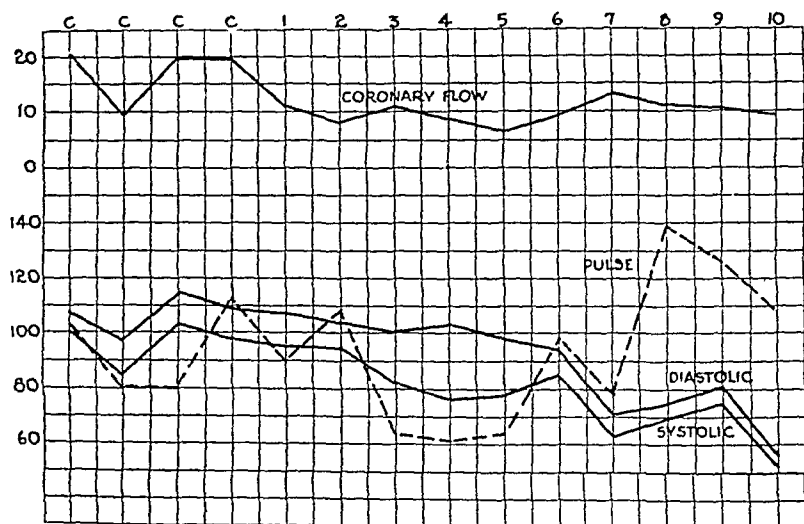


Chart 5—This graph illustrates the type of result (in dog 60) that is not considered to indicate a decrease in volume of coronary flow due to the action of digitalis (whole leaf preparation 1). The volume of coronary flow decreases, but there is an accompanying fall in blood pressure and in pulse rate. This represents the type of result classified as "decrease in coronary flow accounted for by fall in blood pressure or pulse rate." An accidental interference with the venous return flow occurred at the second control reading.

A composite graph showing the results in the control series and in the series to which whole leaf preparation 1 was given is presented in chart 6. In this the average deviation at each period from the control value is plotted. In spite of a level or slightly increased pulse rate and an increased systolic and diastolic pressure in the animals receiving digitalis, the coronary flow in this series averages decidedly less than in the control series.

To be certain that the results obtained were not due to properties inherent in the preparation used, a second market preparation of the

whole leaf, referred to as whole leaf preparation 2, was used in twelve dogs. The results, which are summarized as follows, are substantially the same as with the first preparation.

	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	7
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	3
Increase in coronary flow accounted for by increase in blood pressure or pulse rate	2

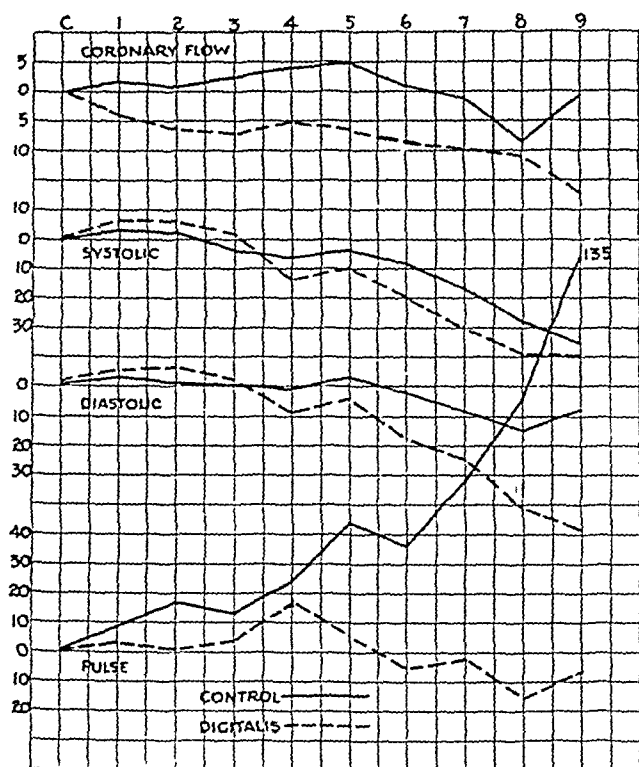


Chart 6—A composite graph, comparing the results obtained in the series to which whole leaf preparation 1 was administered with the results obtained in the control series receiving no medication. The average deviation from the last control reading at each ten minute interval is plotted from the same base line. The broken lines represent the course followed by the coronary flow and by its determining factors, systolic and diastolic blood pressure and pulse rate, in the series to which digitalis was administered. The solid line represents the course of the coronary flow and its determining factors in the control series. A decreased coronary flow with digitalis is observed, in spite of an increase in the factors that would normally cause an increased flow.

A third digitalis preparation was used, the exact composition of which we do not know. It is a popular and generally used preparation of the whole leaf, which has been subjected to a special process in the course of manufacture. The preparation used in these experiments was a market preparation, standardized to a strength comparable to



the two preceding preparations The results obtained were quite different from those of the two preceding preparations, as indicated by the following summary

	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	1
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	5
Increase in coronary flow accounted for by rise in blood pressure or pulse rate	5

There was evidence of vasoconstriction in only one experiment, and in the others the coronary flow followed normally the changes in blood pressure and pulse rate

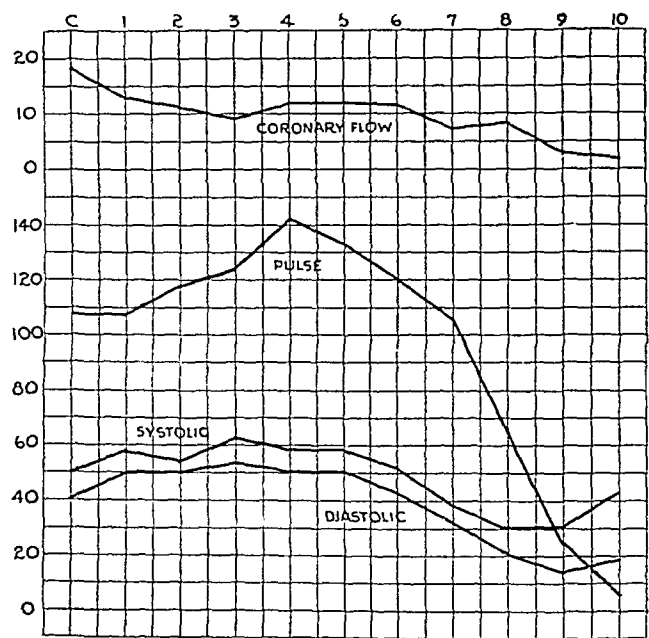


Chart 7—Result of a single experiment (dog 186) in which whole leaf preparation 2 was used The coronary flow decreases in spite of an increase in the factors that would normally cause it to increase

These results were so divergent from those obtained with the other preparations that it was felt that the series should be enlarged, and several months later a second series of eleven dogs was tested, with the following results

	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	0
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	4
Increase in coronary flow accounted for by increase in blood pressure or pulse rate	6
Increase in coronary flow unaccounted for by increase in blood pressure or pulse rate	1

The results of the second series confirmed those obtained in the first series, and would seem to indicate a qualitative difference in the preparations

We are able to offer no explanation for the difference in the action of this preparation. We have carefully considered the possibility of experimental error.

As will be shown later, no decrease of the volume of coronary flow was observed in vagectomized or atropinized animals. Because of this observation, it was considered possible that this special preparation did not possess a central action. Accordingly the experimental work of Greene and Peeler<sup>12</sup> was repeated by one of us in conjunction with Miss Ruth Trump. In this experiment the head of a turtle was

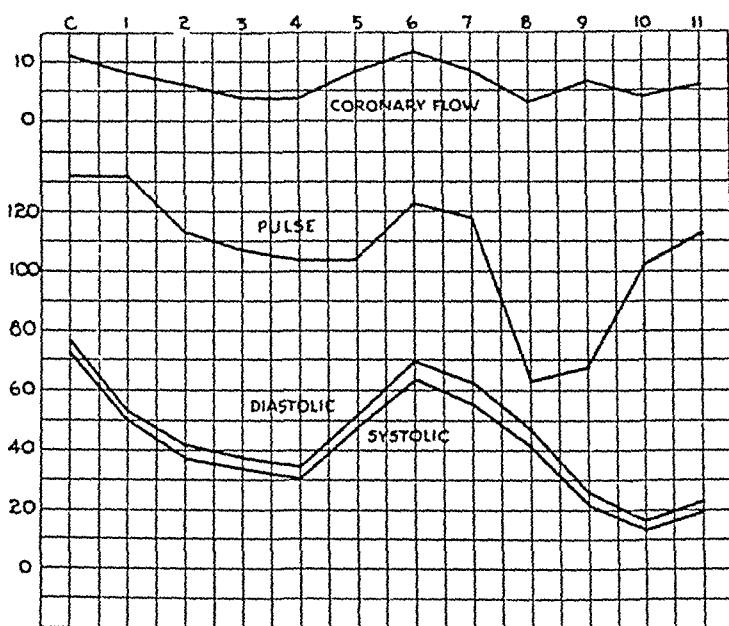


Chart 8—Results of an experiment on a dog (dog 135) to which whole leaf preparation 1 was administered (one tenth of the estimated lethal dose at ten minute intervals) two days after both cervical vagi had been severed. The coronary flow follows the variations in its determining factors as in the control series.

entirely separated from the body, except for the vagus nerves, and the head was perfused with Ringer's solution, to which was added, after a control period, the drug to be tested. Greene and Peeler showed digitalis under these conditions to have a central effect on rate and conductivity after a short latent period. Whole leaf preparation 1 and special preparation 1 gave results identical with those obtained by Greene, and did not differ from each other.

<sup>12</sup> Greene, C. W., and Peeler, J. O. *J. Pharmacol. & Exper. Therap.* **7**: 591, 1915.

OUABAIN

Standard ouabain obtained from the United States Bureau of Standards through Professor Carlson and made up by Professor Van Dyke gave results similar to those obtained with the first two preparations as follows

	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	5
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	4
Increase in coronary flow accounted for by increase in blood pressure or pulse rate	2
Increase in coronary flow unaccounted for by increase in blood pressure or pulse rate	1

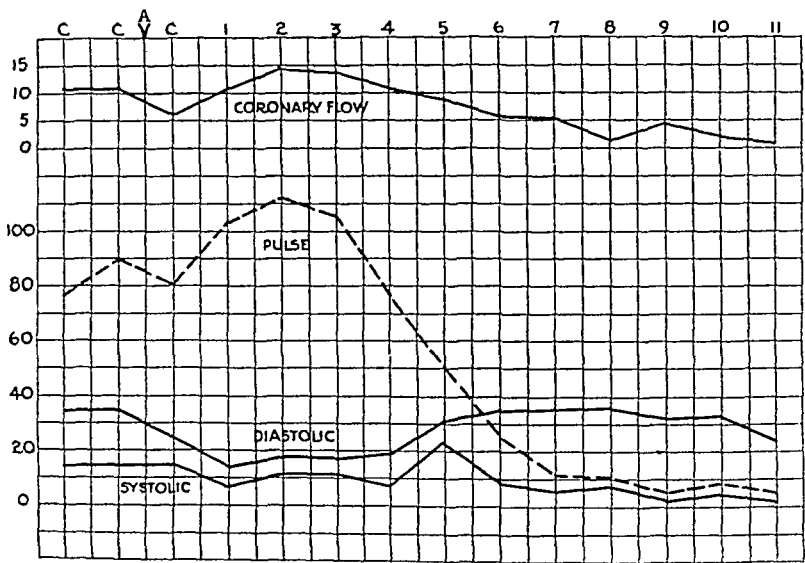


Chart 9—In this experiment 0.2 mg of atropine sulphate per kilogram of weight was administered at A, and one tenth of the estimated lethal dose of whole leaf preparation 1 was given at ten minute intervals, beginning after the last control period at the third (C). There is no evidence of any vasoconstrictor effect of digitalis on the coronary arteries.

Here also evidence of a vasoconstrictor action occurs, although in one of twelve dogs there was an increase in coronary flow without corresponding changes in blood pressure or pulse rate. In a similar series of seven dogs a market preparation of strophanthin was used. The results which are indicated in the following summary were the same as with the standard ouabain, and show evidence of a vasoconstrictor action.

	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	3
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	4

Digitoxin we found very difficult to obtain at the time when these experiments were done. We used two preparations, one of which was obtained from Germany. From the results obtained by Voegtlin and Macht<sup>2</sup> on arterial strips we should have expected the most marked vasoconstrictor effects from crystallized digitoxin. We actually found much less effect on the coronary flow from this preparation. It is unfortunate that we are not more certain of the quality of our digitoxin. Other effects of digitalis obtained from this preparation were variable. The results with each preparation are as follows:

<i>Digitoxin (American)</i>	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	2
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	4
Increase in coronary flow accounted for by increase in blood pressure or pulse rate	2

<i>Digitoxin (German)</i>	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	2
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	5
Increase in coronary flow accounted for by increase in blood pressure or pulse rate	3

In a series of eleven dogs the vagi were cut one or two days before the experiment. There was no evidence of a vasoconstrictor action in these dogs on the administration of whole leaf preparation 1. The results in this series were as follows:

<i>After Vagotomy</i>	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	0
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	7
Increase in coronary flow accounted for by rise in blood pressure or pulse rate	4

With the use of atropine, 0.2 mg per kilogram of weight, before the experiment, similar results were obtained:

<i>After Atropine</i>	Cases
Decrease in coronary flow unaccounted for by fall in blood pressure or pulse rate	0
Decrease in coronary flow accounted for by fall in blood pressure or pulse rate	2
Increase in coronary flow accounted for by increase in blood pressure or pulse rate	8

The results of the experiments on vagectomized and atropinized animals would suggest the possibility at least of an effect on the vagus. Against a purely central effect are the observations with special preparation 1 and the experiments showing that this preparation of the drug has a central effect in the turtle as regards at least rate and conductivity. Against a central action also are the positive results obtained by other authors on artery strips and on the isolated heart. The section of the vagus and the atropine evidently introduce an element not explained in these experiments.

#### COMMENT

The experiments reported seem to indicate that digitalis does have an effect that decreases the coronary flow. This decrease is observed under conditions of pulse rate and blood pressure that would normally tend to increase the volume of coronary flow.

It is at least possible that there was a decrease in coronary flow in part of the cases in which the blood pressure and the pulse rate fell. However, it is not to be expected that such a vasoconstrictor action would be present in all experimental cases or in all clinical cases. Such an action is not to the biologic advantage of the animal, and it is to be expected that it would be offset by some protective reflex mechanism. Greene<sup>13</sup> and others have stressed the ease with which vasodilator effects may be obtained by nerve stimulation and the difficulty with which vasoconstrictor effects on the coronary arteries are obtained.

Angina pectoris may be assumed to include a large group of cases in which it is probable that vasoconstriction of the coronary arteries occurs as a result of reflexes originating in various sources. Such a reflex vasoconstriction, moreover, is not to the advantage of the patient and does not occur with a normally acting autonomic system, but in persons whose autonomic systems show lowered thresholds and are overlabile. It is in such a group that one would expect a vasoconstrictor action from digitalis to occur on the coronary arteries most readily.

In a large series of clinical cases, as in a large series of experimental animals, digitalis in comparable doses shows a wide divergence of action. The different physiologic effects do not always appear in the normal sequence, or with the same percentage of the lethal dose, or one or another action may not appear at all. The physiologic effect is probably not a simple function, but is conditioned by a great many anatomic and biochemical factors with which we are not as yet familiar.

The coronary flow is also a function of many variable factors, and effect of one isolated factor cannot be predicted. While a vasocon-

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<sup>13</sup> Greene C W. I. Missouri M A 28 466 1931

strictor action cannot be predicted in any case, we feel that there is enough evidence of the presence of such an action to warrant a great deal of caution in the use of digitalis in coronary disease

#### CONCLUSION

In a series of experiments on dogs, evidence was elicited indicating that digitalis bodies may exert a vasoconstrictor action on the coronary arteries

# RELATION OF SUGAR TO CHOLESTEROL IN THE BLOOD

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It is known that in diabetes mellitus there is often a distinct increase in the level of both the blood sugar and the plasma cholesterol. The relationship between the fluctuations of these two substances in the blood in diabetes mellitus is not constant, as shown by many observers (Boyd,<sup>1</sup> Joslin, Bloor and Gray,<sup>2</sup> Gray,<sup>3</sup> Rabinowitch,<sup>4</sup> and White and Hunt<sup>5</sup>). McCrudden and Sargent<sup>6</sup> studied the blood cholesterol and sugar in a number of pathologic states and were not able to demonstrate any constant correlation. There are several complicating factors which may arise in the course of diabetes mellitus that may raise either the blood sugar or the plasma cholesterol or both. Thus it is established that severe acidosis and diabetic coma, malnutrition, overnutrition and a high fat intake continued over a long period may bring about a hypercholesterolemia (Bloor<sup>7</sup>), though the blood sugar may be elevated in some of these conditions, but not in others. It becomes obvious that an unvarying direct relationship between dextrose and cholesterol in the blood does not occur because of the numerous widely differing factors that may influence them.

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This research was aided by a grant from the Josiah Macy, Jr., Foundation.

Read before the Association of American Physicians, Atlantic City, N. J., May 4, 1932.

From the Department of Medicine, New York Post-Graduate Medical School and Hospital.

1 Boyd, G. L. Blood Fat in Diabetic Children, *Am J Dis Child* **36** 298 (Aug.) 1928.

2 Joslin, E. P., Bloor, W. R., and Gray, H. The Blood Lipoids in Diabetics, *J N M A* **69** 375 (Aug. 4) 1917.

3 Gray, H. Lipoids in 1,000 Diabetic Bloods with Special Regard to Prognosis, *Am J M Sc* **168** 35, 1924.

4 Rabinowitch, I. M. The Cholesterol Content of the Blood Plasma in Diabetes Mellitus, *Arch Int Med* **43** 363 (March) 1929, The Cholesterol Content of Blood Plasma in Juvenile Diabetes, *ibid*, p. 372.

5 White, P., and Hunt, H. Cholesterol of the Blood of Diabetic Children, *New England J Med* **202** 607, 1930.

6 McCrudden, F. H., and Sargent, C. S. Comparison of the Glucose and Cholesterol Content of Blood, *J Biol Chem* **33** 387, 1918.

7 Bloor, W. R. Diet and the Blood Lipoids, *J Biol Chem* **95** 663, 1932.

It remains to be determined whether the change of the blood sugar level in itself, regardless of acidosis, malnutrition, overnutrition and similar conditions, has any bearing on the concentration of the plasma cholesterol. Such a determination has an obvious and distinct bearing on the clinical interpretation of the cholesterol values, especially in diabetes mellitus.

The present study is an analysis of the concomitant fluctuations in the blood sugar and plasma cholesterol following the ingestion of 100 Gm of dextrose in ninety-five persons who were normal or gave evidence of either mild diabetes mellitus or renal glycosuria. The test subjects fasted for approximately fourteen hours and were then given 100 Gm of dextrose in solution by mouth. Synchronous determinations of blood sugar and plasma cholesterol were carried out before the ingestion of dextrose and subsequently at intervals of twenty, forty, sixty and one hundred and twenty minutes. The blood sugar was determined by the Folin-Wu<sup>8</sup> method, and the plasma cholesterol by the Sackett modification of Bloor's method<sup>9</sup>.

The maximal deviation of plasma cholesterol within five hours while the subjects were fasting or during twenty-four hours while they were consuming three meals a day was found to be 7.8 per cent, according to the researches of Biuger and Somach<sup>10</sup>. All variations in the plasma cholesterol in excess of these limits were regarded as fluctuations for which the consumption of the dextrose was responsible. Table 1 details the figures for thirteen cases in which the plasma cholesterol dropped more than 20 per cent, as calculated from the control level, and table 2 presents the data from nine cases in which the plasma cholesterol rose more than 30 per cent. From these tables it is evident that the variations in plasma cholesterol after the ingestion of dextrose may be marked, and that they do not always occur in the same direction.

It is important to check the relation of the type of blood sugar curve, or the dextrose tolerance, to the changes in the plasma cholesterol. If a blood sugar of 120 mg per hundred cubic centimeters two hours after the taking of dextrose is regarded as normal and a higher blood sugar as indicating a prolonged curve, significant of a diminished dextrose tolerance, it becomes apparent from tables 1 and 2 that, although a rise or a fall of the plasma cholesterol may occur with a normal or a prolonged sugar curve, a drop of cholesterol is more commonly found with the higher glycemia at the end of the two hour period.

8 Folin, O., and Wu, H. System of Blood Analysis, *J Biol Chem* **41** 367, 1920.

9 Sackett, G. E. Modification of Bloor's Method for the Determination of Cholesterol in Whole Blood or Blood Serum, *J Biol Chem* **64** 203, 1925.

10 Bruger, M., and Somach, I. The Diurnal Variations of the Cholesterol Content of the Blood, *J Biol Chem* **97** 23, 1932.



TABLE 1—Cases in Which the Plasma Cholesterol Dropped More Than 20 Per Cent After the Ingestion of 100 Gm of Dextrose \*

Fasting Control		Minutes after Ingestion of Dextrose, 100 Gm								Duration of Blood Sugar Curve
		20		40		60		120		
Blood Sugar	Plasma Choles terol	Blood Sugar	Plasma Choles terol	Blood Sugar	Plasma Choles terol	Blood Sugar	Plasma Choles terol	Blood Sugar	Plasma Choles terol	
95	173	139	166	86	<u>105</u>	80	127	69	117	Normal
96	183	128	<u>144</u>	145	156	124	166	100	146	Normal
108	204	164		230	<u>144</u>	230	237	140	222	Prolonged
94	270	147	214	158	<u>188</u>	158	200	143	<u>188</u>	Prolonged
93	191	142	186	174	167	211	<u>75</u>	150	150	Prolonged
113	189	152	171	190	162	208	<u>136</u>	158	160	Prolonged
114	221	147	194	169	192	188	<u>163</u>	172	168	Prolonged
124	154	179	147	214	158	254	158	254	<u>120</u>	Prolonged
143	222	218	245			250	<u>175</u>	260	184	Prolonged
203	185	205	179	339	175	285	161	278	<u>139</u>	Prolonged
143	560	165	464	217	272	250	256	300	<u>224</u>	Prolonged
156	194	247	183	291	185	308	175	333	<u>157</u>	Prolonged
227	266	416	240	625	<u>206</u>	500	211	418	245	Prolonged

\* The minimal figure for plasma cholesterol is underlined

\* This table gives an indication of the extent to which the plasma cholesterol may fall

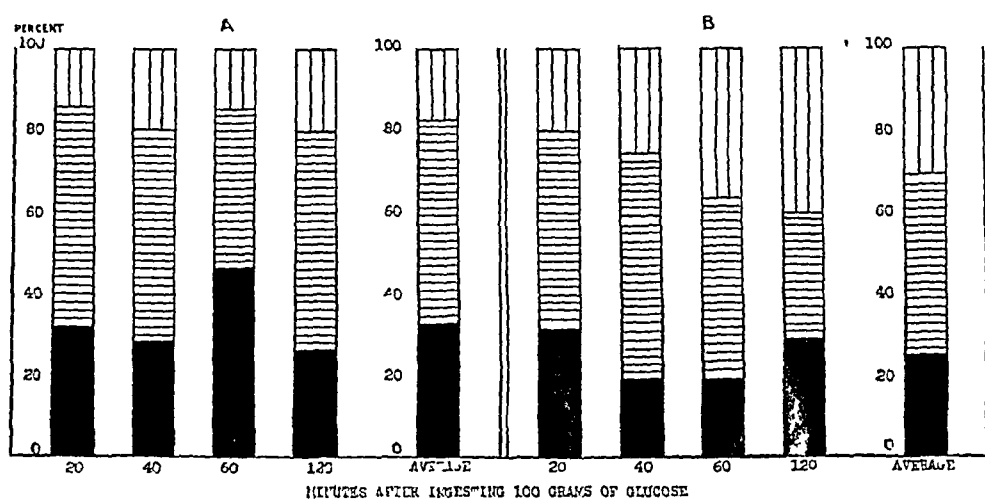
TABLE 2—Cases in Which the Plasma Cholesterol Rose More Than 30 Per Cent After the Ingestion of 100 Gm of Dextrose \*

Fasting Control		Minutes after Ingestion of Dextrose, 100 Gm								Duration of Blood Sugar Curve
		20		40		60		120		
Blood Sugar	Plasma Cholesterol	Blood Sugar	Plasma Cholesterol	Blood Sugar	Plasma Cholesterol	Blood Sugar	Plasma Cholesterol	Blood Sugar	Plasma Cholesterol	
79	193	143	258	130	<u>300</u>	111	230	105	202	Normal
100	120	111	<u>160</u>	133	120	125	120	111	109	Normal
95	136	136	136			167	158	115	<u>188</u>	Normal
91	157	107	176	167	<u>230</u>	176	213	120	200	Normal
77	169	142	<u>222</u>	183	176	183	162	135	175	Prolonged
75	208	120	222	188	<u>286</u>	231	283	150	275	Prolonged
86	193	125	240			176	<u>300</u>	153	230	Prolonged
125	214	214	260			259	<u>286</u>	300	278	Prolonged
150	158	211	147	300	167	319	163	375	<u>219</u>	Prolonged

\* The maximal figure for plasma cholesterol is underlined

\* This table gives an indication of the height to which the blood cholesterol may rise

These points are possibly shown more clearly in chart 1. While every one recognizes that 120 mg per hundred cubic centimeters is a normal blood sugar finding two hours after a test meal of 100 Gm of dextrose, there are many who believe that the same value in three hours is a sufficient criterion, or that 140 mg two hours after taking the dextrose is all that is required to establish normal carbohydrate tolerance. Taking these interpretations of what constitutes the criterion for a normal dextrose tolerance into consideration, the ninety-five cases studied have been divided into two groups: those in which the blood sugar at the end of two hours was 140 mg or less per hundred cubic centimeters (fifty-eight cases) and those in which it was above 140 mg in two hours (thirty-seven cases). The variations in the plasma cholesterol after ingestion of dextrose are analyzed on this basis in the chart. A study of



Variations in plasma cholesterol after ingestion of dextrose. *A*, blood sugar 140 or less in two hours (fifty-eight cases), *B*, blood sugar above 140 in two hours (thirty-seven cases). The vertical lines indicate a decrease, the horizontal lines, no change, and the solid black, an increase in plasma cholesterol. Controls indicate that the maximal deviation of plasma cholesterol is 78 per cent. The height of the columns indicates the percentage of instances in each group.

this chart reveals that after the rise and fall of blood sugar following the ingestion of 100 Gm of dextrose: 1. The plasma cholesterol may remain constant, rise or fall. 2. The plasma cholesterol remains unchanged in about one half of the cases. 3. Although a diminution or an increase in the plasma cholesterol may occur, whether the dextrose tolerance is normal or impaired, it is evident that the plasma cholesterol is more frequently lowered when the blood sugar is markedly elevated, as is seen in the cases with diminished sugar tolerance sixty and one hundred and twenty minutes after the ingestion of dextrose, and is most often raised when the dextrose tolerance is normal, as is seen in these cases sixty minutes after the ingestion of dextrose.

## COMMENT

There is a relation between the level of the blood sugar and that of the plasma cholesterol. As the blood sugar rises after the ingestion of dextrose, the plasma cholesterol may remain constant or increase or diminish appreciably. The factors that bring about these changes in the plasma cholesterol concentration are probably in part compensatory osmotic phenomena, as suggested by the fact that the level of the blood sugar and that of the plasma cholesterol are often inversely proportional. This fact, however, fails to account for the many instances in which the plasma cholesterol is elevated in these observations. The speed and efficiency of the oxidation of dextrose and the storage of dextrose as glycogen in the liver and in other tissues suggest themselves as possible factors that will influence the level of the plasma cholesterol. The results of the present experiments cannot be interpreted as definite evidence in this regard, but they do point to the fact that the metabolism of dextrose has a far-reaching influence on the level of the plasma cholesterol. Furthermore, in diabetes mellitus, although it is evidently true, as has been frequently noted, that the blood sugar and plasma cholesterol do not always vary directly or inversely, there is a relationship that must be considered in the clinical interpretation of these substances in the blood.

Remesow and Matrossowitsch<sup>11</sup> carried out simultaneous sugar and cholesterol determinations of the blood after feeding, and after intravenous injection, of cholesterol in dogs and rabbits. They also obtained similar sugar and cholesterol curves after the injection of epinephrine, insulin and other substances. They find that the dextrose and the cholesterol always rise or fall in the blood in diametrically opposite directions (except after injections of insulin). From this they conclude that cholesterol is invariably converted into carbohydrate when it exists in excess in the blood. This does not agree with the results reported in this paper, since the relation between the blood sugar and plasma cholesterol did not exhibit the constancy reported by Remesow and his collaborator. Furthermore, as studies in the laboratory have shown, the ingestion of dextrose and the subsequent rise in blood sugar are accompanied by variations in the concentration of urea, sodium chloride, the plasma proteins and probably other substances, this would make it appear far-fetched to deny that efforts on the part of the body to maintain an osmotic equilibrium do not play a large part in causing the fluctuations of all of these substances. That cholesterol by some chemical process assumes carbohydrate characteristics is another matter,

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<sup>11</sup> Remesow, I, and Matrossowitsch, D. Experimentell-chemische Studien über den Lipoidstoffwechsel. II Mitteilung. Blutzuckerkurven bei Carnivoren und Herbivoren während der experimentellen Lipämie. III Mitteilung. Über die Veränderungen des Lipoidstoffwechsels, hervorgerufen durch Adrenalin, Insulin und einige Alkaloide, *Ztschr f d ges exper Med* **77** 67, 1931.

and is a proposal to which one should not agree without more definite proof on the subject than has been submitted hitherto

#### CONCLUSIONS

A rise in the dextrose of the blood, brought about by the ingestion of 100 Gm of dextrose, is accompanied by variations in the concentration of the plasma cholesterol. The plasma cholesterol may remain constant or may rise or fall appreciably. Compensatory osmotic phenomena may account for some of these fluctuations but not for all of them.

# CONGESTIVE HEART FAILURE

## XVII THE MECHANISM OF DYSPNEA ON EXERTION

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To the fundamental studies of Sir James MacKenzie we are indebted for the concept that in cardiac disease the patient's response to effort constitutes the best index to prognosis and the most accurate guide to therapy. Although most clinicians would agree that the patient's dyspnea, that is his subjective respiratory distress, is the most important clinical phenomenon in cardiac disease, an adequate explanation of the mechanism of this symptom has yet to be offered.

The generally accepted idea of respiratory control involves the assumption that any muscular effort that is sufficiently severe to increase the ventilation is necessarily associated with shifts toward acidity in the blood or in the respiratory center itself. According to Haldane,<sup>1</sup> Winterstein<sup>2</sup> and numerous other authors, the activity of the respiratory center is dependent almost entirely on the hydrogen ion concentration of the arterial blood. The recent studies of Gesell<sup>3</sup> have demonstrated the importance of the blood flow through the respiratory center in the regulation of breathing and have led to the more or less general recognition of the fact that increased acidity of either the arterial or the venous blood may be responsible for greater ventilation. According to these ideas, one has to assume that when a normal person performs muscular exercise, his breathing increases either because of a pouring of acid into the blood stream or because of a lessened circulation to the brain. In the former case, alterations in the composition of the blood passing to the brain are postulated, in the latter case, changes in the state of the blood passing from the brain must be assumed.

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<sup>1</sup> Haldane, J S. *Respiration*, New Haven, Conn., Yale University Press, 1922 p 185

<sup>2</sup> Winterstein H. *Die Regulierung der Atmung durch das Blut*, Arch f d ges Physiol **138** 167, 1911

<sup>3</sup> Gesell R. *The Chemical Regulation of Respiration*, Physiol Rev **5** 551, 1925

## DYSPNEA

The application of these concepts to the problem of dyspnea produced by exertion in patients with disease of the heart has led to a widely accepted belief that the patient with an abnormal heart suffers during exertion from either actual or relative diminution in the output of his heart. That such patients exhibit, after a given amount of exertion, greater ventilation than do normal persons has generally been attributed to a diminution in cerebral blood flow and a consequently greater shift toward acidity in the respiratory center. As examples of this point of view, one may quote Means,<sup>4</sup> who wrote

The fundamental fault responsible for cardiac dyspnea is obviously to be found not in the nature of the blood but in the rate at which it is pumped, in the heart itself. Into the varieties of heart disease we need not go. The factors leading to dyspnea are common to all. The important point is that the heart, either because of increased work, fatigue or degeneration, is unable to maintain an adequate rate of blood-flow. In brief, then, we may assume that in cardiac disease there may, through slow blood flow, be delay both in getting oxygen in and carbon dioxide out.

Meakins and Davies<sup>5</sup> said

We are pursuing further work on this question but we would suggest that cardiac failure of this character is due to an incomplete ventricular systole as a consequence of which the circulation rate is greatly and progressively diminished. Therefore, a general cellular oxygen want and cellular carbon dioxide acidosis would develop with all the typical symptoms of dyspnea, weakness, exhaustion, precordial discomfort and even loss of consciousness.

It may be noted, however, that no one has yet reported data obtained from analysis of the blood at rest and during mild exertion which indicate that the alterations in the composition of the blood postulated in these views are actually present.

On the contrary, in a recent study made by Cullen, Harrison, Calhoun, Wilkins and Tims,<sup>6</sup> the following results were obtained:

1 Neither during nor after exercise were significant alterations observed in the hydrogen ion concentration, carbon dioxide content, carbon dioxide pressure or oxygen content of *arterial* blood. The exercise was mild but sufficient to cause a well marked increase in ventilation and to cause slight or moderate dyspnea in persons with cardiac disease.

2 Likewise, muscular exertion produced no changes in the composition of the blood from the *internal jugular vein*.

<sup>4</sup> Means, J. H. Dyspnea, *Medicine* **3** 388, 1924.

<sup>5</sup> Meakins, J. C., and Davies, H. W. *Respiratory Function in Disease*, Edinburgh, Oliver & Boyd, 1925, p. 328.

<sup>6</sup> Cullen, G. E., Harrison, T. R., Calhoun, J. A., Wilkins, W. E., and Tims, M. M. Studies in Congestive Heart Failure. XIII The Relation of Dyspnea of Exertion to Oxygen, Carbon Dioxide and Hydrogen Ion Concentration of the Blood, *J. Clin. Investigation* **16** 807 (Oct.) 1931.

3 Ammonium chloride caused a relatively great decrease in  $p_{\text{H}}$  and in carbon dioxide content, but caused only a slight increase in ventilation, whereas mild muscular activity caused a relatively striking increase in ventilation and no significant change in blood acidity or gases

Chart 1, showing some of these points, is illustrative of but one of a fairly large series of observations in which similar results were encountered

This work demonstrated that the increase in ventilation which occurs in the performance of mild exercise, and which ordinarily suffices to produce discomfort in persons with cardiac disease, is not due to changes in the composition of the blood or to diminution in the blood supply to the respiratory center. The cause of dyspnea on mild exertion had to be sought elsewhere.

The valuable observations of Peabody and his co-workers<sup>7</sup> have indicated the great importance of the vital capacity as a measure of the tendency toward dyspnea. With these studies as a basis, Harrison, Turley, Jones and Calhoun<sup>8</sup> attempted to arrive at a somewhat more quantitative measurement of this symptom. The results indicated that the ratio  $\frac{\text{ventilation}}{\text{vital capacity}}$  constitutes a fairly certain numerical guide. In other words, dyspnea tends to result from any process that diminishes the vital capacity or from any cause that increases ventilation.

*Diminished Vital Capacity as Cause of Dyspnea*—In persons with cardiac disease the vital capacity is usually lower than in normal persons. This diminution tends to cause dyspnea in two different ways.

(a) *Per se* it lowers the respiratory reserve and hence means that for any given level of ventilation dyspnea is more likely to occur.

7 Peabody, F W. Clinical Studies on the Respiration. I The Effect of Carbon Dioxid in the Inspired Air on Patients with Cardiac Disease. Arch Int Med **16** 846 (Nov) 1915, II The Acidosis of Chronic Nephritis, *ibid* **16** 955 (Dec) 1915, III A Mechanical Factor in the Production of Dyspnea in Patients with Cardiac Disease, *ibid* **20** 433 (Sept) 1917. Peabody, F W, and Wentworth J A. IV The Vital Capacity of the Lungs and Its Relation to Dyspnea, *ibid* **20** 443 (Sept) 1917. Peabody, F W, Wentworth, J A, and Barker, B I. V The Basal Metabolism and the Minute-Volume of the Respiration of Patients with Cardiac Disease, *ibid* **20** 468 (Sept) 1917. West, H F. VI A Comparison of Various Normal Standards for the Normal Vital Capacity of the Lungs, *ibid* **25** 306 (March) 1920. Peabody, F W, and Sturgis, C C. VII The Effect of General Weakness and Fatigue on the Vital Capacity of the Lungs, *ibid* **28** 501 (Nov) 1921. Sturgis, C C, Peabody, F W, Hall, F C, and Fremont-Smith, F. VIII The Relation of Dyspnea to the Maximum Minute-Volume of Pulmonary Ventilation, *ibid* **29** 236 (Feb) 1922. Peabody, F W, and Sturgis, C C. IX The Effect of Exercise on the Metabolism, Heart Rate and Pulmonary Ventilation of Normal Subjects and Patients with Heart Disease, *ibid* **29** 277 (March) 1922.

8 Harrison, T R, Turley, F C, Jones, E, and Calhoun, J A. Congestive Heart Failure. X The Measurement of Ventilation as a Test of Cardiac Function, Arch Int Med **48** 377 (Sept) 1931.

(b) A decrease in vital capacity also tends to cause a reflex increase in breathing. This was shown by Harrison, Cullen, Calhoun, Wilkins and Pilcher.<sup>9</sup> Their findings may be briefly summarized as follows:

1 Experimental diminution of the vital capacity of dogs by any one of several methods resulted in an increased rate and volume of breathing, provided the vagus nerves were intact. After these nerves had been cut, the same procedures were not ordinarily accompanied by changes in respiration.

2 During these procedures analyses were made of arterial blood and of venous blood from the brain. A slight or moderate reduction of vital capacity was not accompanied by significant changes in the acid-base condition or gases of the blood, but was associated with increased ventilation in animals with intact vagi. A

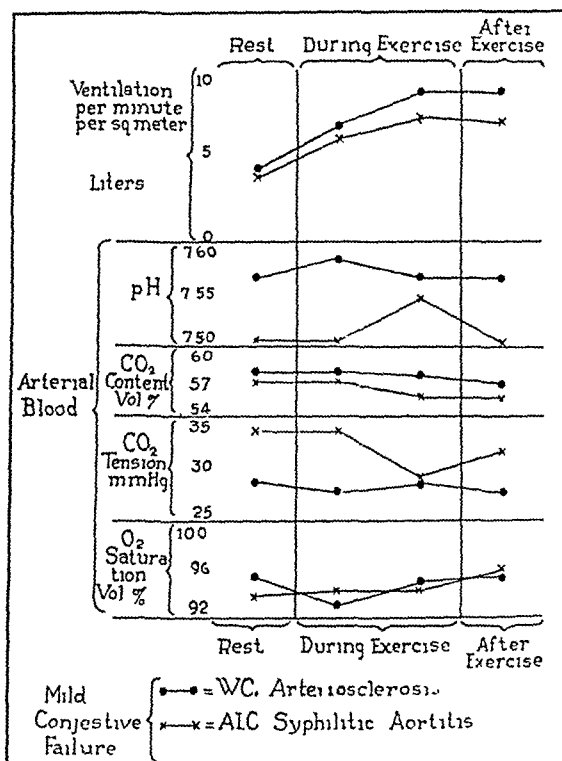


Chart 1—The chart is constructed from the data of Cullen, Harrison, Calhoun, Wilkins and Tims. The values for pH and carbon dioxide represent determinations on serum, whereas the analyses for oxygen content were done on whole blood. In both patients the ventilation during and after exercise was considerably greater than at rest. The arterial blood did not become more acid and its carbon dioxide tension did not increase. Likewise significant alteration in the oxygen and carbon dioxide content did not occur.

more marked decrease in vital capacity caused deficient aeration of the blood and resulted in increased ventilation even when the vagus nerves had been cut.

3 No evidence of consistent alteration in cerebral blood flow was found in the experiments.

<sup>9</sup> Harrison, T. R., Cullen, G. E., Calhoun, J. A., Wilkins, W. E., and Pilcher, C. Studies in Congestive Heart Failure. XV. Reflex Versus Chemical Factors in the Production of Rapid Breathing, *J. Clin. Investigation* 11:133, 1932.



This study indicated clearly that diminished vital capacity causes a reflex increase in ventilation, the afferent path being through the vagus nerves. The average values for the vital capacity of the subjects portrayed in charts 2 and 3 were 2.3 liters per square meter for the normal persons and 1.6 liters per square meter for the patients. It is therefore evident that the increase in rate and volume of respiration which was observed at rest in these patients can be attributed to the reflex effects of a diminished vital capacity.

Since the effects of relatively slight diminutions in vital capacity were so striking, it was thought at first that the greater ventilation during mild exertion might be due to a diminution in vital capacity brought

TABLE 1—*The Effect of Muscular Exertion on the Vital Capacity*

			Vital Capacity, Liters	
			Rest	Immediately After Exercise
Normal Subjects				
W	E	W	4.35	1.20
T	B		3.05	3.05
P	R	H	4.20	4.35
H	W		1.45	4.45
W	G	H	4.40	4.30
M	M	T	3.55	3.55
B	W		3.70	3.55
H	I		3.50	3.70
Persons with Cardiac Disease				
I	C		3.05	2.80
C	C		2.45	2.65
P	G		2.75	2.60
W	C		2.95	2.90
M	M		3.15	3.05
L	F		2.95	2.95
L	C		1.95	1.95

about by muscular activity. Actual observations concerning this point showed that this was not the case (table 1).

These observations seem to clarify the rôle of diminished vital capacity in the production of dyspnea on exertion. Even at rest the vital capacity is decreased and this predisposes to dyspnea, but, since the vital capacity does not undergo further diminution during exercise, it is evident that the cause of the actual appearance of dyspnea during exertion must be sought in changes in the ventilation.

*Increased Ventilation as a Cause of Dyspnea*—The ventilation in patients with cardiac disease is greater than normal at rest, during exertion and after exertion. This is illustrated in chart 2, in which are plotted the average results of the measurements of ventilation in a group of nine persons with cardiac disease as compared with four normal persons, the values being expressed in terms of ventilation per square meter. The curves of the respiratory rate are similar in the two groups except that the patients with cardiac disease breathed faster throughout the

observations. The ventilation curves show that the respiratory minute volume of the patients was also greater during each minute. This was not the only deviation from the normal, for (chart 3) the degree of increase in ventilation was, after the first minute of the exercise, greater in the patients than in the controls. Furthermore, the percentage increase in ventilation after the exercise (chart 3, upper part) was also greater in the patients, and the return to the resting level of ventilation was slower in the patients than in the controls. The actual average figures for the total excess ventilation were in the normal subjects 11.2 liters or 2.9 times the resting value and in the patients 15.7 liters or 3.4 times the resting value. From these findings it is clear that an adequate explanation for these changes in ventilation—and consequently a satis-

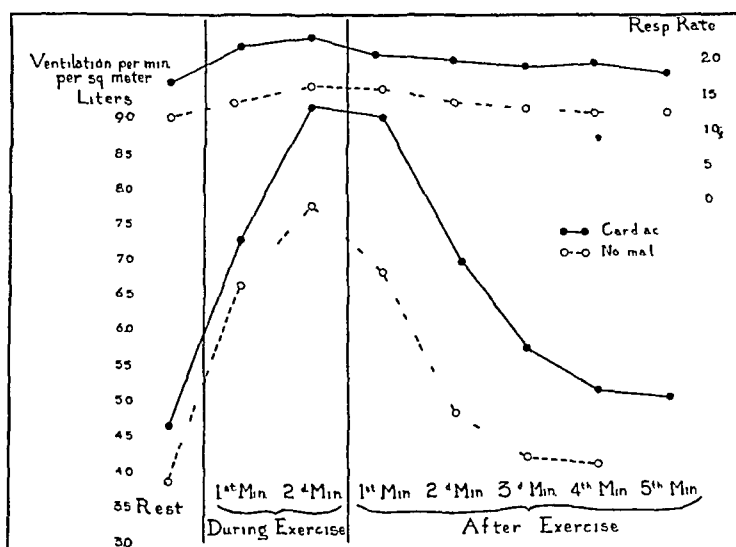


Chart 2—The two upper curves represent the respiratory rates of normal subjects and patients with cardiac disease, respectively. Throughout the observations the latter persons breathed faster, and after exercise their respiratory rates remained elevated somewhat longer. The two lower curves represent ventilation. The patients had greater ventilation at rest, a greater degree of increase in ventilation during exercise and a slower return to normal after the exercise than was the case in the normal subjects. In both groups the ventilation was greater during the second than during the first minute of the work.

factory understanding of the mechanism of dyspnea—involves the answer to two questions:

1. Why is mild exertion (of degree insufficient to produce alteration in the composition of the blood) associated with an increase in ventilation both in patients with cardiac disease and in normal persons?

2. Why does exercise cause an increase in ventilation which is greater (actually and relatively) in patients with cardiac disease than in normal subjects?

## CLINICAL AND EXPERIMENTAL DATA

We have already pointed out that studies of the hydrogen ion concentration and of the gases of the blood failed to reveal changes during or after exercise that was mild but that caused increased breathing and dyspnea in patients with cardiac disease. Therefore it seemed evident that there were two possible causes of the increase in ventilation (a) It was due to some chemical stimulus other than alterations in the blood gases or the hydrogen ion concentration, or (b) the effect was of 'nervous' origin.

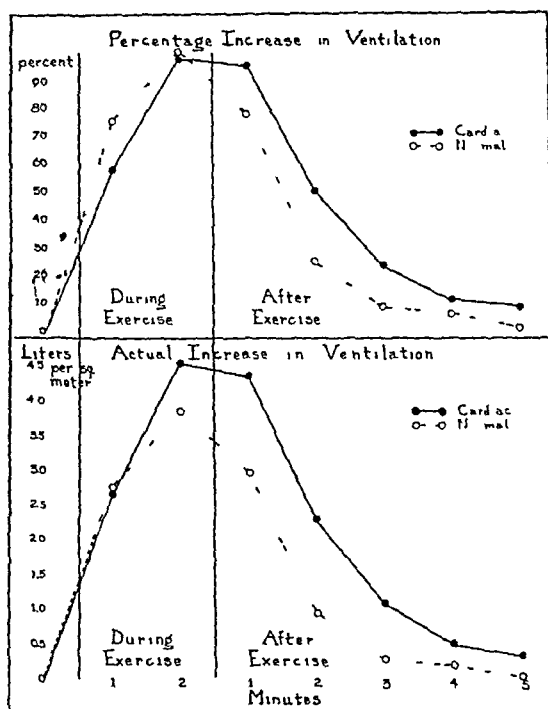


Chart 3—In the lower portion are depicted the actual increases in ventilation. During the first minute of the exertion the two groups had about the same degree of increase, but in the subsequent minutes the patients had a greater increase. It is noteworthy that the ventilation of the patients was still above the resting value five minutes after the exercise. In the upper portion the percentage increase in ventilation is shown. During the exercise the control subjects had a relatively greater (though actually less) increase in ventilation, whereas after the exercise the ventilation of the patients was not only actually but relatively increased to a greater degree.

The first of these hypotheses seemed to us unlikely for a number of reasons, but it was felt that it should be put to experimental test.

*A Evidence that the Increased Ventilation Produced in Man by Mild Muscular Exercise Is Not of Chemical Origin*—As subjects, three patients with cardiac disease were used. In some instances the expired air was collected in a Tissot spirometer and the respirations were

counted, while in others a graphic record of the breathing was obtained with a Benedict spirometer and the ventilation was calculated from the tracing

1 The Effect of Active Movements of the Extremities on the Ventilation The movements consisted of rapidly opening and closing the hands or of rotating the feet Care was taken, for reasons given

TABLE 2—*The Effect of Muscular Movements on the Ventilation of Patients with Cardiac Disease*

Subject	Diagnosis	Ventilation per Minute, Liters		
		Before	During	After
A The Effect of Active Movements with the Circulation Intact				
S J	Emphysema, chronic bronchitis, mild congestive failure	7 78	9 05	8 54
		8 32	9 36	8 73
R J	Hypertension, mild congestive failure	6 66	9 16	6 86
W C	Hypertension, mild congestive failure	7 90	10 80	9 98
	Average	7 67	9 59	8 53
B The Effect of Active Movements with the Circulation Impeded by Pressure				
S J	Emphysema, chronic bronchitis, mild congestive failure	8 26	9 70	8 70
		8 32	10 60	9 15
R J	Hypertension, mild congestive failure	8 12	8 74	7 28
W C	Hypertension, mild congestive failure	7 48	10 80	10 38
	Average	8 04	9 96	8 88
C The Effect of Passive Movements with the Circulation Intact				
S J	Emphysema, chronic bronchitis, mild congestive failure	9 25	12 45	10 46
		8 32	10 20	7 90
R J	Hypertension, mild congestive failure	6 45	7 70	6 87
W C	Hypertension, mild congestive failure			
	Average	8 01	10 12	8 41
D The Effect of Passive Movements with the Circulation Impeded by Pressure				
S J	Emphysema, chronic bronchitis, mild congestive failure	9 00	10 70	9 54
		8 73	11 23	8 73
R J	Hypertension, mild congestive failure	6 24	8 12	6 45
W C	Hypertension, mild congestive failure			
	Average	7 99	10 01	8 28
E The Effect of Releasing the Pressure and Restoring the Circulation after Muscular Movements				
S J	Emphysema, chronic bronchitis, mild congestive failure	8 52		9 98
		8 11		9 36
R J	Hypertension, mild congestive failure	6 87		7 70
		6 66		6 87
W C	Hypertension, mild congestive failure	8 92		9 56
	Average	7 82		8 69

later to insure that the muscles above the elbows and knees did not participate in the movement

As shown in part A of table 2 the ventilation of each of the subjects was greater during the movements than it was before or after them. The different subjects, though showing similar qualitative affects, varied in the degree of response. This was probably dependent on the fact that some of them made stronger movements than did the others. None

of the subjects knew what was expected of him and hence it is not conceivable that psychic influence could have been responsible for the change in breathing

2 The Effect of Active Movements of the Extremities on the Ventilation When the Circulation to and from the Moving Muscles Is Blocked In order to attempt to determine whether the increase in ventilation was or was not due to chemical alterations in the blood

TABLE 3—*The Effect of Muscular Movements on the Ventilation of Normal Men*

Subject	Portion of Body Moved	Respiratory Rate			Ventilation per Minute, Liters		
		Before	During	After	Before	During	After
A The Effect of Active Movements with the Circulation Intact							
W E W	Hands and feet	15	23	17	7 70	12 06	8 53
F R H	Hands and feet	8	22	8	6 85	18 40	7 00
G L C	Feet	15	16	15	7 24	8 73	8 10
F B	Hands	14	18	14	7 56	12 30	8 70
B The Effect of Active Movement with the Circulation Impeded by Pressure							
W E W	Hands and feet	16	27	17	7 70	13 20	8 32
F R H	Hands and feet	8	18	9	6 49	15 32	5 95
G L C	Feet	17	18	16	8 32	8 52	7 70
T B	Hands	13	20	13	8 56	14 10	8 37
C The Effect of Passive Movements with the Circulation Intact							
W L W	Hands and feet						
F R H	Hands and feet						
G L C	Feet	16	19	18	7 70	8 94	7 70
T B	Hands	11	17	11	8 71	11 30	8 71
D The Effect of Passive Movements with the Circulation Impeded by Pressure							
W E W	Hands and feet						
F R H	Hands and feet						
G E C	Feet	19	17	14	8 11	8 74	7 28
T B	Hands	14	18	15	8 71	11 95	9 02
E The Effect of Releasing the Pressure and Restoring the Circulation after Muscular Movements							
W E W	Hands and feet	16		16	8 11		9 78
F R H	Hands and feet	8		7	5 76		6 66
G E C	Feet	16		14	7 28		7 28
F B	Hands	15		11	8 37		8 12

returning to the general circulation from the exercising muscles and affecting the respiratory center, the observations were repeated but with blood pressure cuffs inflated to 200 mm placed around the proximal portions of the extremities. An effort was made to be certain that no movement took place in the muscles proximal to the cuff. The findings are shown in table 2, part B, and it can be seen that under these conditions the ventilation increased during the exercise to about the same degree as was the case when there was no impediment to the circulation.

In order to determine whether this rather surprising result was a representative physiologic response or whether it was in some way

related to the presence of cardiac disease in the subject, the observations were repeated on normal men. Here again the breathing increased, when muscular movements were performed, regardless of whether or not the circulation to the moving parts was intact (table 3, parts A and B).

In charts 4 and 5 are shown respiratory records from a normal subject and from a patient with cardiac disease, respectively. In each instance the respiratory rate and ventilation increased during muscular movements whether or not the circulation was intact.

These observations admitted of two alternative interpretations. Either, (a) since the circulation through the bone was not blocked, the increase in ventilation was due to respiratory stimulation by some chemical substance reaching the general blood stream by means of the veins draining the bone, or (b) the increase in ventilation was of "nervous" and not of "chemical" origin.

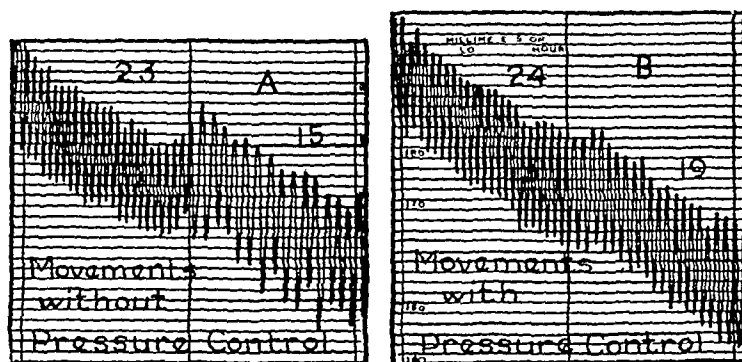


Chart 4—The curve runs from right to left. The distance between two adjacent vertical lines represents one minute. Movements of the hands caused an increase in the respiratory rate and in ventilation whether or not the circulation was intact.

In a later portion of this paper it will be shown that the first hypothesis is untenable because muscular movements in dogs cause an increase in ventilation even when the moving extremity is entirely amputated except for its nerve and vessels and when the latter are clamped (see table 4 and chart 14). Hence the second assumption would seem to be the correct one.

*B. Evidence that the Increased Ventilation Produced in Man by Mild Muscular Movements Is of Reflex Origin*—If the increase in ventilation in the type of exercise investigated is not due to alteration in the composition of the blood, it is presumably of nervous origin. If this is assumed to be true, two alternate explanations present themselves. Either (a) the phenomenon is of cortical origin, i. e., is due to an "overflowing" to the respiratory center of impulses from the motor areas of the cerebrum to the voluntary contracting muscles, or (b) it is a reflex from some part of the moving extremity to the respiratory center.

Krogh and Lindhard<sup>10</sup> found that the ventilation increases abruptly with the beginning of exercise and that this effect comes on too soon to be due to alterations in the hydrogen ion concentration of the blood. Because of the fact that the ventilation increased when the subject remained at rest but was led to expect that work would be performed, these authors concluded that the increase in ventilation was due to irradiation of impulses from the higher centers to the respiratory center.

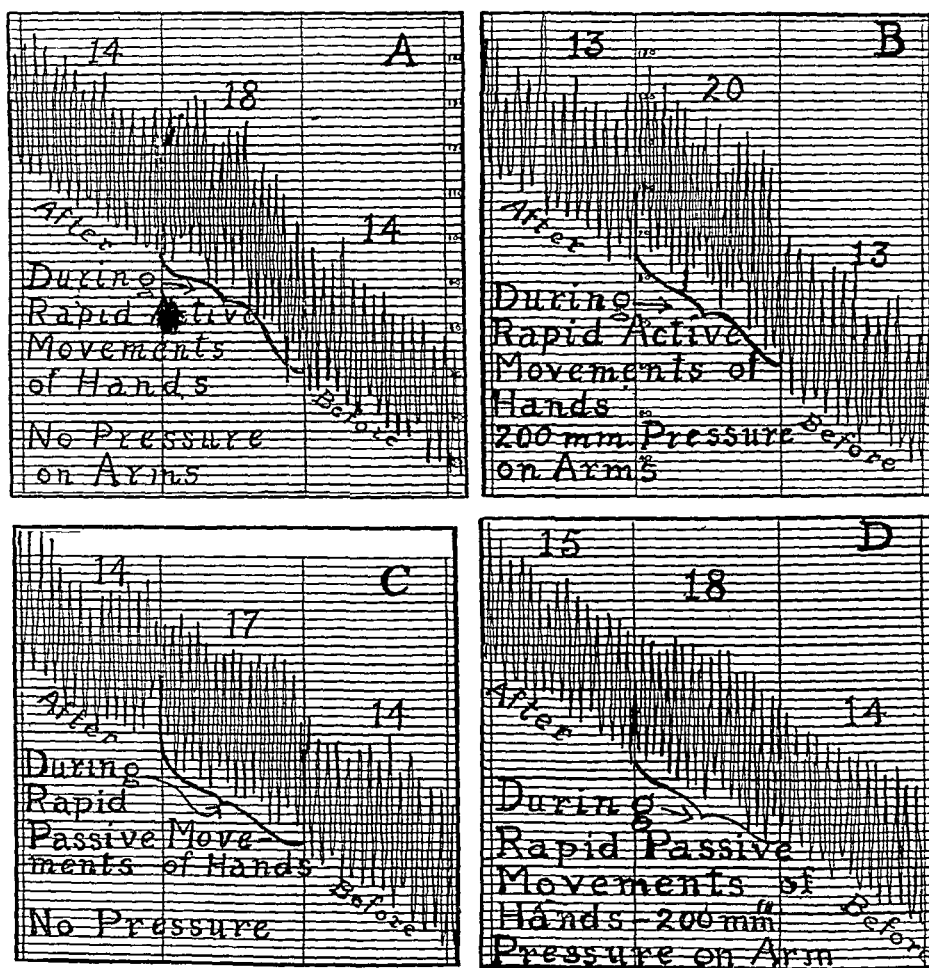


Chart 5—The curve runs from right to left. The numbers refer to respirations per minute. The distance between the vertical lines represents one minute.

rather than to reflexes. In a later study Krogh and Lindhard<sup>11</sup> made observations concerning the effect on the respiration of muscular work that was not voluntary but was induced by electrical stimulation of the muscles. They concluded that in this type of work the immediate

10 Krogh, A, and Lindhard, J. The Regulation of Respiration and Circulation During the Initial Stages of Muscular Work, *J Physiol* **47** 112, 1913.

11 Krogh, A, and Lindhard, J. A Comparison Between Voluntary and Electrically Induced Muscular Work in Man, *J Physiol* **51** 182, 1917.

increase in respiration was of reflex origin, but their observations did not allow them to differentiate clearly between the respiratory effects due to the movements and those due to the electrical current

1 The Effect of Passive Movements of the Extremities on the Respiration When the Circulation to and from the Moving Muscles Is Intact In order to test this matter further we have observed the effect of passive movements The subject was instructed to make no voluntary movements and to relax the extremities which were to be moved In order to distract his attention he was instructed to read throughout the course of the observations The operators of this experiment moved the extremities rapidly either by alternately flexing and extending the hands or by rotating the feet The results are shown in tables 2 and 3, part C and in chart 5, it can be seen that each subject showed an increase in ventilation during the passive movements, the degree of increase being about the same as that found with active movements

2 The Effect of Passive Movements of the Extremities on the Ventilation When the Circulation to and from the Moving Muscles Is Blocked In order to be certain that the increase in ventilation occurring during passive movements was not due to some alteration in the blood, the observations were repeated with pressure around the proximal portions of the extremities As can be seen in tables 2 and 3, part D, the respiratory response was similar to that occurring with passive movements when the circulation was intact

3 The Effect on the Ventilation of Reestablishing the Circulation Through Muscles Which Had Been Exercised While the Circulation to and from Them Was Blocked In order to obtain further information concerning the relative importance of chemical and nervous effects on respiration, the ventilation was observed following the release of the cuffs These had been in place for seven minutes for three minutes before, for one minute during and for three minutes after exercise The results are seen in tables 2 and 3, part E In most of the subjects a slight increase in ventilation occurred when the circulation was reestablished This effect was much less than that obtained by muscular movements In two persons no increase in ventilation occurred when the cuffs were released

*C Proof That the Increase in Ventilation Produced in Dogs by Mild Muscular Movements Is of Reflex Origin*—One might be tempted to believe that the observations which have been reported constituted final proof that, in the type of muscular movements under consideration, the increase in ventilation was due to reflex rather than to chemical factors

We do not believe that such an assumption is justifiable from the data that have been presented, for the following reasons

1 The possibility remains that some blood from the exercising muscles returned to the general circulation through the bones and it might



be argued that this blood was responsible for the changes observed in ventilation in those experiments in which the venous return was obstructed by compression of the proximal portions of the moving extremities

2 It is possible that imperceptible contractions of muscles proximal to the cuffs may have caused alterations in the composition of the blood

In order to meet these objections, experiments were performed on dogs. The animals were given barbitol, approximately 0.3 Gm per kilogram of body weight, intravenously, about one hour before the beginning of the experiment. Tracheotomy was done. In some instances respiration was recorded by having the animal rebreathe oxygen from a Benedict spirometer. When it was desired to obtain accurate measurements of the ventilation a different method was used, the expired air being passed through a two-way tap from which it could be collected in either one of two Benedict spirometers, one of which could be emptied while the animal was breathing into the second.



Chart 6—*A*, passive movement of right leg with intact nerve. *B*, stimulation of peripheral end of left cut sciatic nerve. The curve runs from right to left. The numbers refer to respirations per minute. The distance between the vertical lines represents one minute.

Passive movements were performed at the rate of about three hundred per minute, an effort being made to avoid moving any part of the dog's body other than the extremity in question. This was not entirely possible (except in the final group of experiments in which the hip joint was amputated), as it was often necessary to "shake" vigorously in order to elicit any respiratory response at all. It was found that different animals varied markedly in their response, the degree of increase in ventilation being less in those animals which were most deeply anesthetized and particularly so when in addition they were in a state of severe shock.

1 The Effect of Movements of the Hind Leg with and Without the Cutting of the Sciatic Nerve. Such an experiment is shown in chart 6. Passive movements of the intact right leg caused an increase in respiration. Active movements in the opposite leg—induced by stimulation of the peripheral end of the cut sciatic nerve—had no such effect. However

this experiment was not convincing because the mass of muscle moving was less in the latter than in the former instance

2 The Effect of a Tourniquet Around the Leg on the Respiratory Response to Passive Movements In chart 7 it is shown that the ventilation was increased by passive movements whether or not the vessels were compressed by a tourniquet The tourniquet was tightly drawn and probably obstructed most of the circulation except that through the bone However, since the latter circulation was not occluded, the experiment must be considered inconclusive

3 The Effect of Cutting the Spinal Cord on the Respiratory Response to Passive Movements The animal portrayed in chart 8 showed a definite, although slight, response to movements of the hind-leg and of the fore-leg when the spinal cord was intact (in the charts,

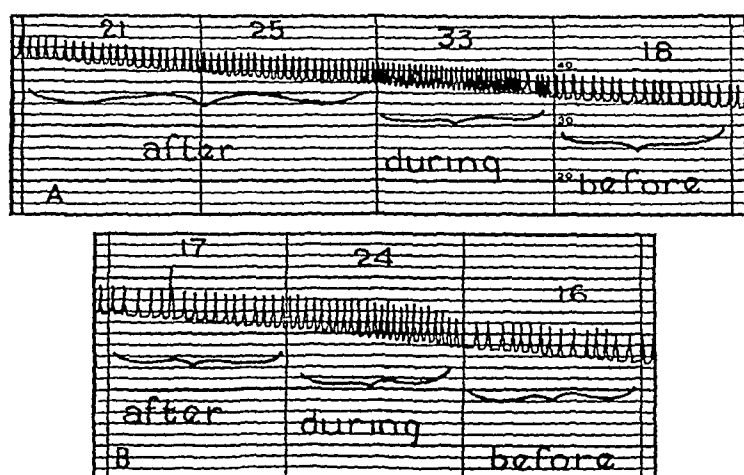


Chart 7—1, passive movements of intact leg B, passive movements of leg-tight tourniquet around all parts of leg except sciatic nerve The curve runs from right to left The numbers refer to respirations per minute The distance between the vertical lines represents one minute

for the sake of convenience in labeling, "leg" refers to the hind-leg and "arm" to the fore-leg) After chordotomy at the level of the sixth dorsal vertebra, the respiration was not affected by passive movements of the hind-leg but became accelerated when the fore-leg was moved

In another animal (chart 9) more striking results were obtained When the spinal cord was intact, well marked effects were obtained by moving the tail, the hind-leg, the fore-leg and the head, in the order of increasing response It was noted that the mass of muscle being moved was least when the tail was moved, more with the hind-leg, still more with the arm and most with the head After the spinal cord had been cut at the fourth dorsal level, passive movements of the fore-leg and of the head gave the same response as before, whereas movements of the hind-leg and of the tail were without effect

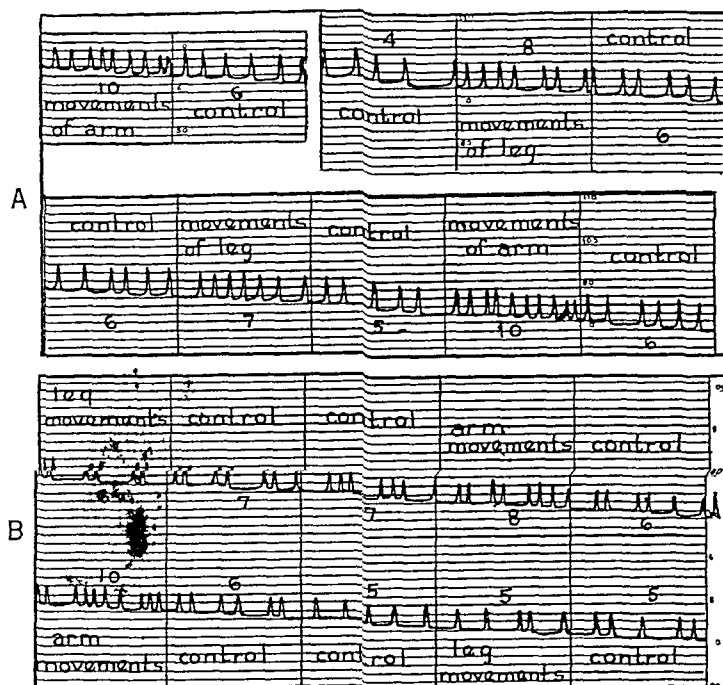


Chart 8—*A*, spinal cord intact *B*, spinal cord cut at sixth dorsal level The curve runs from right to left The numbers refer to respirations per minute The distance between the vertical lines represents one minute

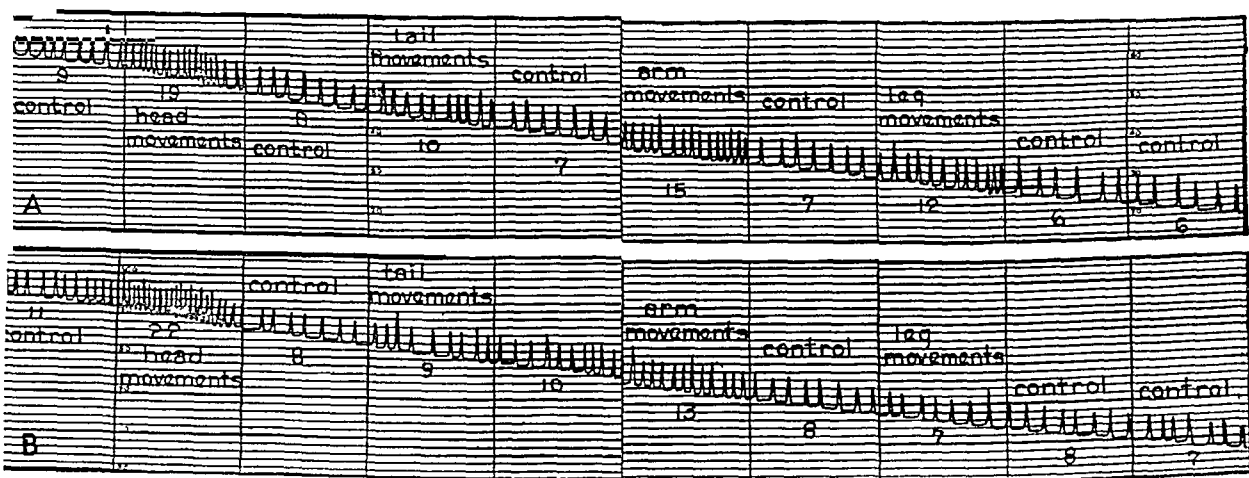


Chart 9—*A*, spinal cord intact *B*, spinal cord cut at fourth dorsal level The curve runs from right to left The numbers refer to respirations per minute The distance between the vertical lines represents one minute

In chart 10, however, is a tracing from an animal that exhibited a well marked increase in ventilation on moving the hind-leg after the spinal cord was cut. This result, which was obtained several times, was surprising. It may be noted that the spinal cord was cut at a lower point in this animal than in the previous ones although the level was above that of the sensory fibers from the legs. Consequently, it was decided to cut the cord at two different levels and note the effect. Such an experiment is shown in chart 11. When the cord was intact, the usual increase in ventilation resulted from moving the various portions. Chordotomy at the level of the eighth dorsal vertebra did not change the response. However, after the cord had been cut at the third dorsal vertebra the respiration did not increase when the tail or hind-leg was moved, but did increase when the head or fore-leg was moved.

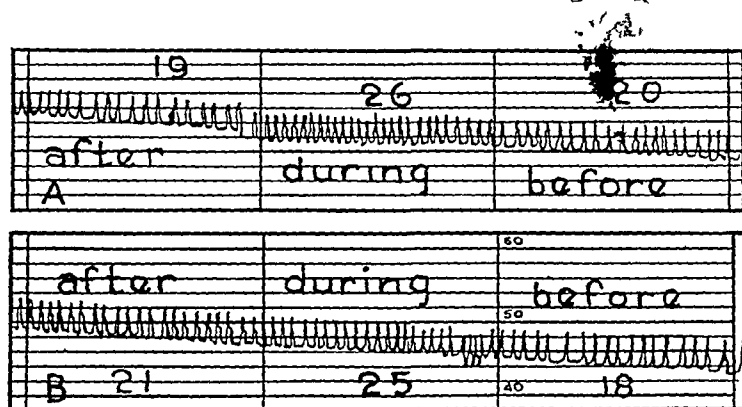


Chart 10—Passive movements of leg with spinal cord cut at ninth dorsal level. The curve runs from right to left. The numbers refer to respirations per minute. The distance between the vertical lines represents one minute.

If one assumed that one was dealing with a reflex, it was believed that these rather curious findings could have one of three possible explanations:

- The afferent path might be through the sympathetic chain.
- The greater degree of shock after chordotomy at the higher levels might abolish the effects from the caudal parts of the body without abolishing those from the cephalic portions.
- The slight movements in the muscles of the abdomen and buttocks when the hind-leg was moved might have been responsible for the effect when the cord was cut at a level lower than the sites of entry of the sensory nerves from these muscles, whereas, with the higher chordotomies, impulses from these areas as well as those from the tail and hind-leg would have been blocked.

In order to determine which of these explanations was correct, further observations were made.

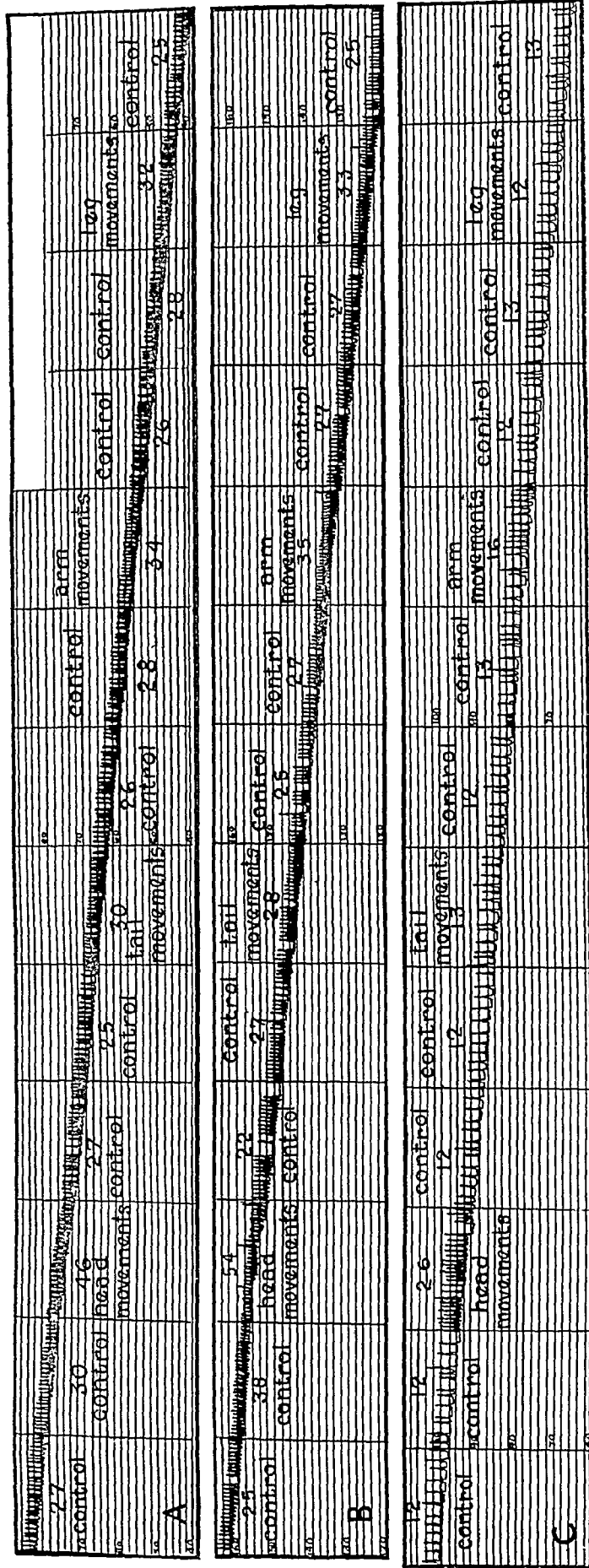


Chart 11—A, spinal cord intact B, spinal cord cut at eighth dorsal level C, spinal cord cut at third dorsal level The curve runs from right to left The numbers refer to respirations per minute The distance between the vertical lines represents one minute

4 The Effect of Unilateral Sympathectomy on the Respiratory Response to Passive Movements Chart 12 is the record from a dog in which the left sympathetic trunk had been cut high in the abdomen. Moving the two hind-legs had practically identical effects on the breathing. It is therefore evident that the pathway for the (hypothetic) reflex under discussion does not lie through the sympathetics.

5 The Effect of Cutting the Posterior Spinal Roots on the Respiratory Response to Passive Movements The animal portrayed in chart

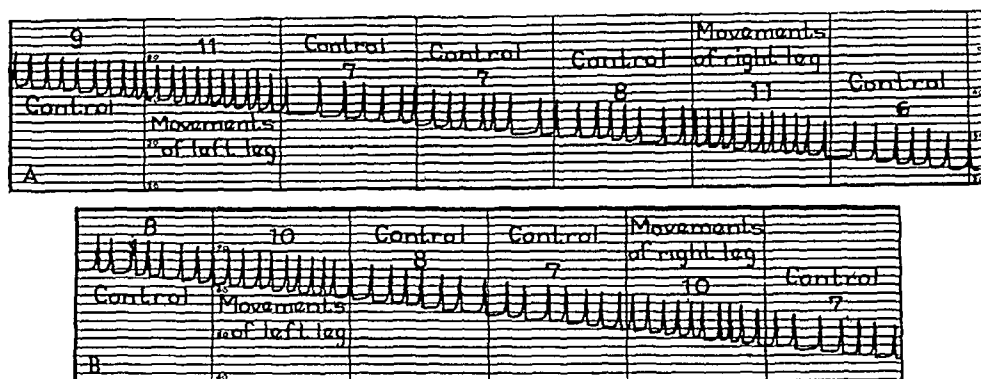


Chart 12—Left abdominal sympathetic cut. The curve runs from right to left. The numbers refer to respirations per minute. The distance between the vertical lines represents one minute.

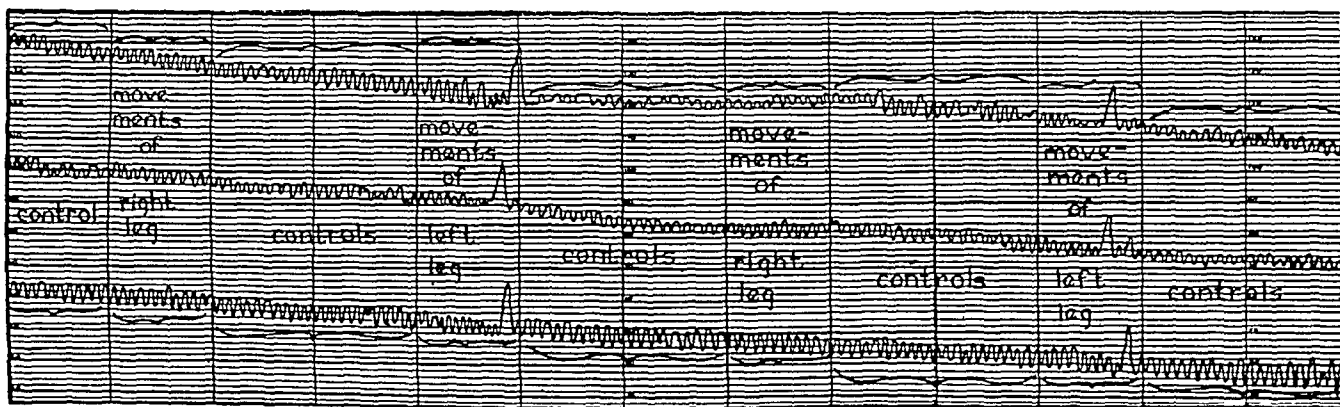


Chart 13—Right posterior roots cut. The curve runs from right to left. The distance between the vertical lines represents one minute.

13 had been operated on about a year previously at which time the lower dorsal, the lumbar and the sacral posterior roots on the right side had been sectioned. It was desired to save the animal, and consequently morphine was used instead of barbitol. The breathing was rather irregular, and a significant, consistent increase in respiratory rate was not obtained by moving either hind-leg. The qualitative response however, was decidedly different, as a deep sigh took place whenever the leg with an intact nerve supply was moved, whereas this did not occur when

the leg that had been deprived of sensation was moved. Again the results speak for some kind of reflex effect, but they are rather inconclusive.

6 The Respiratory Response to Passive Movements of Legs Completely Amputated Except for the Femoral Vessels and the Sciatic Nerve. To the experiments on both men and dogs reported up to this point, two objections can be raised. In the first place, since the bones were intact there is the possibility that the results were influenced by blood returning from the moving extremity. In the second place, it seems likely that the respiration was affected by motions of the muscles of the buttocks and of the abdomen. Although the data that have been presented point toward such an effect being reflex, it might conceivably have been chemical, as it was not possible when dealing with intact extremities to move them without causing some movements higher up, and in no case was the venous return obstructed from these more proximal muscles.

In order to meet these objections, the leg was amputated at the hip joint, and all connections between the leg and the trunk except the femoral vessels and the sciatic nerve were severed. The femur was then tightly clamped in a vise, in such a position that neither the vessels nor the nerves were under tension. This procedure had the double advantage of making it possible to isolate the chemical from the nervous effects and also allowed one to make vigorous passive movements of the leg without causing any movement in the muscles proximal to the leg.

The results are shown in table 4. It can be seen from part A that even when the nerve and vessels were intact, the effects of passive motions were rather slight, being usually much less than in the previous experiments. This is to be attributed to the shock that necessarily ensues following amputation, and also to the fact that the mass of moving vessels was less in the amputated than in the intact legs. It is to be noted that, despite the smallness of the effect, the increase in ventilation occurred in each experiment. (The maximum error of measurement with the small spirometers used is not greater than 0.04 liter and in no instance was the increase in ventilation on passive movements less than three times this possible error.)

Following these observations the femoral vessels were occluded with bull dog clamps and the procedure was repeated (table 4, part B). Again, in each five instances an increase in ventilation resulted although in dog G 13 this was scarcely greater than the error of measurement.

The clamps were then removed from the vessels, the sciatic nerve was cut and, after waiting a few minutes for the respiration to become constant, the procedure was repeated for the third time. In one experiment of the five a slight increase in ventilation resulted. In the remain-

ing four instances moving the leg, when the sciatic nerve had been cut, was without effect even though the blood supply was intact (table 4, part C) These observations seem to prove beyond question that the increase in ventilation produced by such movements is of reflex origin from the moving part

7 The Rapidity of the Response of the Ventilation to Passive Movements As can be seen in almost all charts, the increase in breathing usually occurred immediately after the beginning of passive movements This fact is probably the most convincing evidence obtained that the effect was of reflex rather than of chemical origin

8 The Return of the Ventilation to Normal After the Cessation of Passive Movements In instances in which the increase in ventilation was of small degree the respiration often returned to the previous

TABLE 4—*The Effect of Passive Movements of One Hind-Leg on the Ventilation of Dogs*

Animal	A Leg Amputated Except for Intact Femoral Vessels and Intact Sciatic Nerve			B Femoral Vessels Clamped, Sciatic Nerve Intact			C Sciatic nerve Cut Femoral Vessels Intact		
	Ventilation per Minute, Liters			Ventilation per Minute, Liters			Ventilation per Minute, Liters		
	Before Move ments	During Move ments	After Move ments	Before Move ments	During Move ments	After Move ments	Before Move ments	During Move ments	After Move ments
G 10	3.20	3.38	3.16	3.22	3.34	3.24	3.44	3.52	3.18
G 11	3.58	3.79	3.64	3.86	4.09	3.83	3.85	3.82	3.82
G 12	2.30	3.05	2.35	2.64	3.19	2.77	3.81	3.77	3.67
G 13	1.26	4.41	4.33	4.15	4.19	4.03	2.98	2.76	2.77
G 14	2.02	2.26	2.04	1.82	2.06	1.78	1.62	1.60	1.60

control level as soon as the movements ceased However, when a larger increase in ventilation occurred there was sometimes a "hang-over" effect, the respiration gradually returning to normal over a two or three minute period This phenomenon was rather puzzling and led us to suspect that there might be a delayed chemical effect by means of alterations in the blood, as well as an immediate reflex effect In order to test the matter, observations such as those depicted in chart 14 were made This animal showed a definite increase in ventilation for at least two minutes after the cessation of the movements Since there was no possibility in this instance of any blood from the leg returning to the general circulation, it is obvious that the delayed as well as the immediate increase in ventilation was due, in this instance at least, to nervous influences

On second thought this did not seem surprising It has been shown by Garrey<sup>12</sup> that stimulation of a nerve ganglion produces an increase

12 Garrey, W. E. The Action of Inhibitory Nerves on Carbon Dioxide Production in the Heart Ganglion of Limulus. *J. Gen. Physiol.* 3: 163, 1920



in its metabolism, it produces chemical changes in the ganglion. Hence one might expect a delayed return of the respiration to normal, for time might be required for reversal of the chemical changes induced by stimulation of the respiratory center, whether by reflexes or by other means.

The data that have been presented up to this point seem to indicate beyond question that muscular movements cause reflex stimulation of respiration. They show also that the nervous regulation of breathing is more sensitive than the chemical control. It is apparent that such respiratory adjustments as are made—whether the subject be a normal person or a sufferer from cardiac disease—to the ordinary muscular activities required by a sedentary routine existence are mediated through reflexes. In this regard the patient with cardiac disease and the normal person are similar, it remains for us to consider the respects in which they differ.

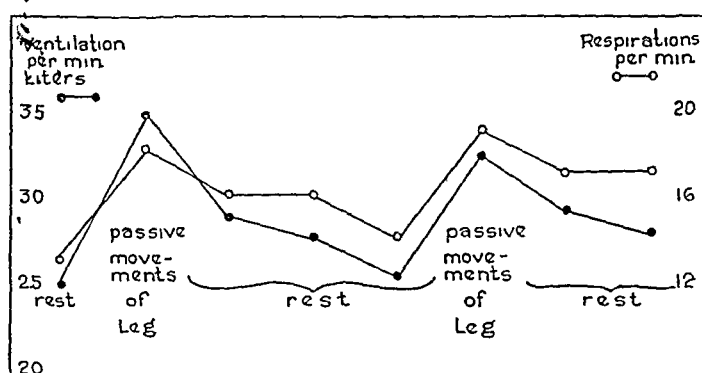


Chart 14—The hind-leg of this dog was amputated except for the femoral vessels, and the sciatic nerve and the vessels were then clamped. Consequently the sciatic nerve was the only possible connection between the leg and the body. Passive movements of the leg resulted in an increase in respiratory rate and in ventilation not only during the movements but for two minutes afterward. The experiment indicates clearly that the increase in ventilation during the movements was of reflex origin, and that after the cessation of movements the delayed return of the ventilation to normal could only have been due to a continued action on the respiratory center of the changes induced in it by the previous stimulation from the reflex effect of the passive movements.

*D Evidence that an Increase in Venous Pressure Produces Reflex Stimulation of Breathing*—The data already reported seem to explain why, in the absence of chemical changes in the blood, muscular effort is accompanied by greater breathing. However, they do not explain why persons with cardiac disease usually have a greater increase in ventilation than do normal subjects on the performance of the same task. Bambridge<sup>13</sup> demonstrated that a rise in pressure in the right auricle

<sup>13</sup> Bambridge, F. A. The Influence of Venous Filling upon the Rate of the Heart, *J. Physiol.* **1** 65, 1915.

and great veins caused a reflex increase in pulse rate. It occurred to us that there might be a similar reflex effect on respiration, and this hypothesis was tested on dogs.

1 The Effect on Respiration of Increasing the Venous Pressure by Infusion of Fluid. In the first group of experiments the effect of

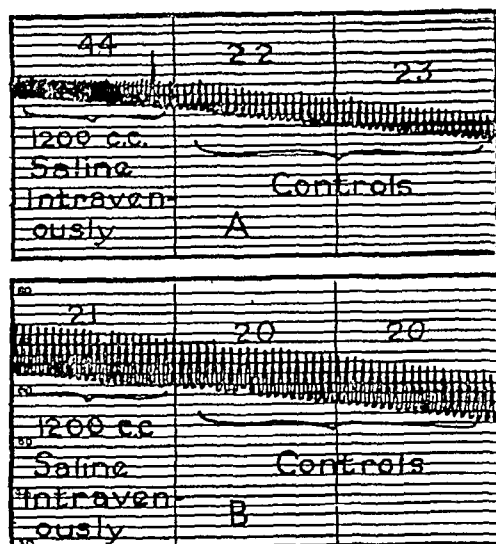


Chart 15—The curve runs from right to left. The distance between two adjacent vertical lines represents one minute. Infusion of physiologic solution of sodium chloride caused a marked increase in respiratory rate and ventilation when the vagus nerves were intact (A) but not when they were cut (B).

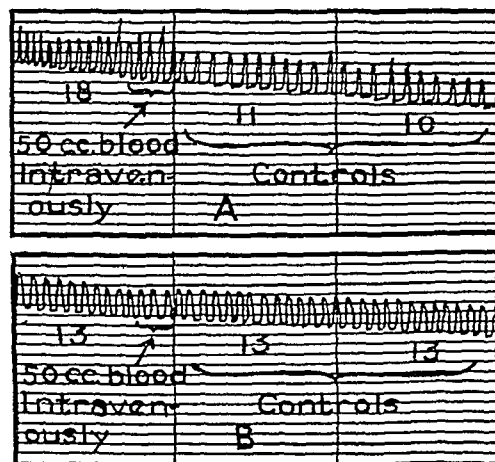


Chart 16—The curve runs from right to left. The distance between two adjacent vertical lines represents one minute. Infusion of as little as 50 cc of defibrinated blood caused a definite increase in respiratory rate and ventilation, provided the vagi were intact. A, vagi intact; B, vagi cut.

suddenly increasing the venous pressure by rapid infusions of fluid into the external jugular vein was noted. The results are shown in table 5 and in charts 15 and 16. Infusions of Ringer's solution, physiologic

solution of sodium chloride and blood all caused an increase in the ventilation and respiratory rate, provided the vagus nerves were intact. When the vagi were cut, no such effect was noted except when citrated blood

TABLE 5—*The Effect on Respiration of Increasing Venous Pressure by Infusion of Fluid*

Animal*	Fluid Used	Amount of Fluid Injected, Cc	Duration of Infusion, Seconds	Before Infusion		Immediately after Infusion		Vagus Nerves
				Ventilation per Minute, Liters	Respirations per Minute	Ventilation per Minute, Liters	Respirations per Minute	
1	Ringer's solution	1,200	60	4.55	26	7.12	42	Intact
2	F	1,200	40	2.57	18	4.64	40	Intact
3	Physiologic solution of sodium chloride	1,200	80	2.28	22	3.19	44	Intact
		1,200	80	4.14	20	4.34	21	Cut
4	Citrated blood	50	10	1.45	14	2.11	17	Intact
	Citrated blood	50		1.86	18	2.73	22	Intact
	Citrated blood	50		2.48	20	3.19	22	Intact
	Bled	300	180	3.19	22	2.46	17	Intact
	Citrated blood	50	10	2.96	11	4.64	14	Cut
	Citrated blood	50	10	4.06	14	5.64	17	Cut
5	Physiologic solution of sodium chloride	50	10	1.99	24	2.82	34	Intact
	Physiologic solution of sodium chloride	50	10	2.59		2.82	34	Intact
	Physiologic solution of sodium chloride	50	10	2.33	25	2.65	32	Intact
	Physiologic solution of sodium chloride	50	10	1.24	4	1.24	4	Cut
	Physiologic solution of sodium chloride	50	10	1.32	4	1.34	4	Cut
	Citrated blood	50	10	1.16	3	1.71	5	Cut
6	Defibrinated blood	50	10	1.37	11	2.28	22	Intact
	Defibrinated blood	50	10	1.62	13	1.59	13	Cut
15†	Physiologic solution of sodium chloride	50	10	1.66	16	1.66	16	Intact
	Physiologic solution of sodium chloride	50	10	2.04	19	2.07	20	Intact
	Physiologic solution of sodium chloride	50	10	2.16	13	2.16	13	Cut
16†	Physiologic solution of sodium chloride	50	20	1.58	17	1.41	17	Intact
	Physiologic solution of sodium chloride		20	1.49	18	1.57	19	Intact
	Physiologic solution of sodium chloride		20	1.36	6	1.42	6	Cut
17†	Physiologic solution of sodium chloride	50	15	0.91	11	0.91	11	Intact
	Physiologic solution of sodium chloride	50	15	1.49	12	1.37	12	Cut

\* In the first six experiments the injections were made into the external jugular vein, with the cannula pointing toward the heart. In experiments 15 and 16 the injections were made into the same vein with the cannula directed away from the heart. In experiment 17 the cannula was in the inferior vena cava and pointed away from the heart.

† Reverse injection.

was used. It is evident that citrate causes chemical stimulation of breathing (animals 4 and 5, table 5). Defibrinated blood caused an increase in ventilation when the vagi were intact but no such effect when these nerves were cut.

These observations led us to believe that the increase in breathing was of reflex origin. In order to determine the source of the reflex, experiments were performed in which the pressure was raised in the veins but not in the heart. A cannula was inserted into the external jugular vein as far down as possible in the neck, and was directed away from the heart. Injecting fluid into the external jugular vein, and hence via the cerebral veins into the general circulation, had no effect on the breathing (table 5, animals 15 and 16). Similarly, when the cannula was placed in the inferior vena cava close to the diaphragm and pointed away from the heart, injecting fluid did not increase the ventilation (table 5, experiment 17). It therefore seemed probable that the

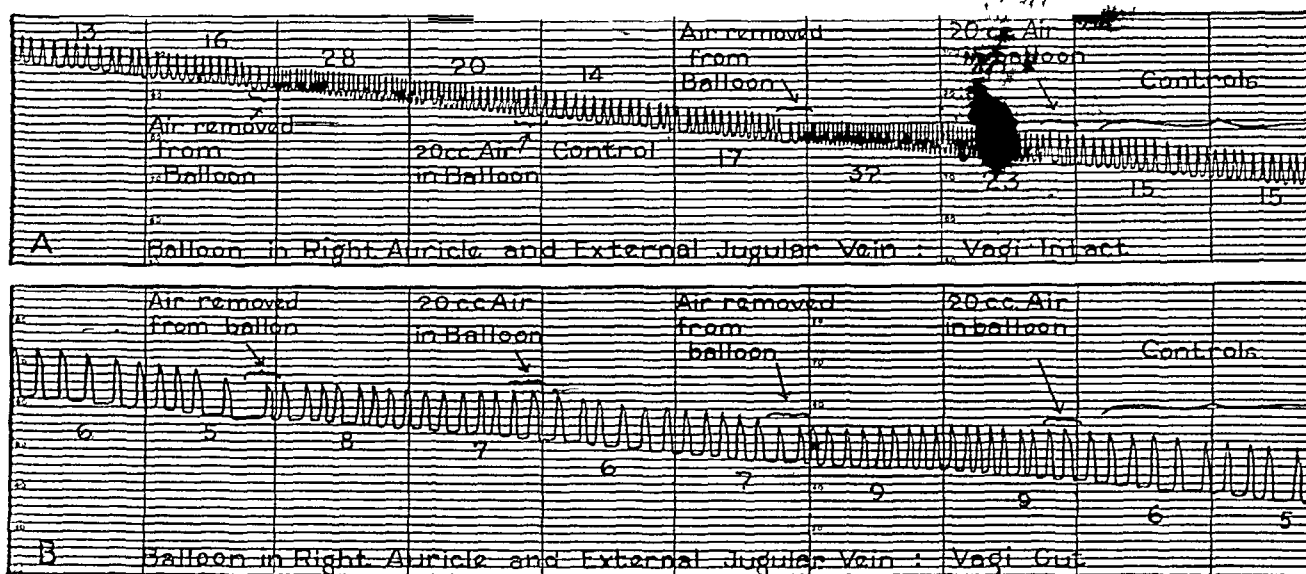


Chart 17—The curve runs from right to left. The distance between two adjacent vertical lines represents one minute. *A*, inflation of the balloon with 20 cc of air caused a well marked increase, and deflation caused a decrease of ventilation. *B*, after vagotomy the effects were much less striking.

respiratory response to injection of fluid was a reflex from the heart or from the great veins very near the heart.

2 The Effect on Respiration of Increasing the Venous Pressure by Distention of a Balloon in the Right Auricle. In order to test the matter further, additional observations were made. By means of a small rubber catheter and a condom an improvised empty balloon into which air could be injected was introduced into the right auricle either through the external jugular vein or through the inferior vena cava. The results are shown in table 6 and figure 17. So long as the vagi were intact, introducing air into the balloon caused an increase in ventilation and respiratory rate, whereas the reverse effects occurred when the air was removed from the balloon. When the vagus nerves were cut the same procedures

either were without effect or produced much less striking results (Bainbridge observed that vagotomized animals might show a slight response in pulse rate to a rise in venous pressure, the afferent path in this instance being by way of the sympathetic nerves. Some of our animals, even after vagotomy had a slight increase in respiration when the venous pressure was increased, but the effect was never marked and was often absent.)

TABLE 6—*The Effect on Respiration of Increasing the Venous Pressure by Injecting Air into a Rubber Balloon in the Right Auricle*

Animal	Position of Balloon	Procedure	Before		After		Vagus Nerves
			Ventilation per Minute, Liters	Respiratory Rate	Ventilation per Minute, Liters	Respiratory Rate	
7	Right auricle external jugular vein	20 cc. of air in balloon	2.50	16	3.78	29	Intact
		Air removed from balloon	3.78	29	2.18	29	
		20 cc. of air in balloon	2.62	15	3.98	32	
		Air removed from balloon	3.98	32	1.88	14	
		20 cc. of air in balloon	1.88	14	3.37	28	
		Air removed from balloon	3.37	28	1.72	13	
		20 cc. of air in balloon	1.37	6	1.45	7	Cut
		Air removed from balloon	1.49	8	1.14	5	
8	Right auricle inferior vena cava	10 cc. of air in balloon	1.87	41	2.18	48	Intact
		Air removed from balloon	2.18	48	1.87	41	
		10 cc. of air in balloon	1.87	41	2.23	49	
		Air removed from balloon	2.23	49	1.68	37	
		10 cc. of air in balloon	1.88	14	1.88	14	Cut
		Air removed from balloon	1.83	14	1.68	14	
		10 cc. of air in balloon	1.68	14	1.56	13	
		Air removed from balloon	1.56	13	1.56	13	
14	Right auricle external jugular vein	20 cc. of air in balloon	2.48	48	3.53	57	Intact
		Air removed from balloon	3.53	57	1.87	41	
		20 cc. of air in balloon	1.87	41	3.62	53	
		Air removed from balloon	3.62	53	2.02	39	
		20 cc. of air in balloon	1.65	10	1.32	8	Cut
		Air removed from balloon	1.32	8	1.16	7	
		20 cc. of air in balloon	1.16	7	1.32	8	
		Air removed from balloon	1.32	8	1.16	7	
13	Right auricle inferior vena cava	15 cc. of air in balloon	0.93	10	1.52	21	Intact
		Air removed from balloon	1.52	21	0.93	9	
		15 cc. of air in balloon	3.14	19	2.82	17	Cut
		Air removed from balloon	2.82	17	2.82	17	

The latter experiments indicate clearly that the increase in ventilation that occurred when fluid was injected could not have been due to augmentation of blood flow, as the balloon would tend to have the opposite effect. It seems clear that the increase in breathing is a reflex from the right side of the heart (and possibly from the cardiac ends of the great veins). The reflex is set off by an increase in the venous pressure or distention of the heart or both, and its afferent path is through the vagus nerves.

These observations are in accord with those of Heymans and Heymans,<sup>14</sup> who demonstrated the existence of respiratory reflexes from the heart through the vagus nerves, and also with the findings of Sutton and Lueth,<sup>15</sup> who found that distention of the left ventricle caused dyspnea in the dog. Bainbridge recorded the respiration in some of his experiments, and did not observe marked changes on increasing the venous pressure. This may have been due to the fact that his animals received morphine, which tends to diminish the sensitivity of the respiratory center to stimulation.

E *The Effect of Exertion on the Venous Pressure of Normal Subjects and of Persons with Cardiac Disease*—The observations just reported indicate that a rise in venous pressure in the dog causes reflex stimulation of respiration. It occurred to us that such a reflex effect might furnish the explanation for the fact that persons with cardiac disease have a greater increase in ventilation than do normal subjects on performing the same exertion.

Schott<sup>16</sup> measured the rise in venous pressure in a series of persons before and after muscular exertion, which consisted of holding one leg upright until the subject became fatigued. He noted absent or minimal increases in normal persons, but patients with cardiac disease had a well marked rise in venous pressure. We have made somewhat similar observations which were carried out as follows:

The subject sat quietly in a comfortable chair for from ten to twenty minutes. A needle was inserted into the median basilic vein, minimal stasis being used. A series of readings of the venous pressure were then made according to the method of Moritz and Tabora.<sup>17</sup> Then, while an observer counted from a stop watch the subject moved the feet outward to two blocks 65 cm apart and inward until the feet touched each other at a rate of thirty complete movements (out and in) per minute for two minutes. Measurements of venous pressure were made every thirty to sixty seconds during the exercise and for five minutes thereafter. The needle was then withdrawn from the vein, the face mask was put on and the ventilation was measured during corresponding rest and exercise periods. (At first we attempted to measure the venous pressure and the ventilation simultaneously, but because of the resistance to the face mask, which caused a slight but measurable rise in the venous pressure, it was found more satisfactory to measure the two functions separately.)

14 Heymans, C, and Heymans, J. F. Stimulation et inhibition reflexes des mouvements respiratoires de la tête "isolée" du chien, *Compt rend Soc de biol* 95 1118, 1926.

15 Sutton, D. C., and Lueth, H. C. Pain, *Arch Int Med* 45 827 (June) 1930.

16 Schott, E. Die Erhöhung des Druckes im venösen System bei Anstrengung als Mass für die Functionstüchtigkeit des menschlichen Herzens, *Deutsches Arch f klin Med* 108 537, 1912.

17 Moritz, F., and Tabora, D. Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen. *Deutsches Arch f klin Med* 93 475, 1910.

Observations were made on three normal males and on five compensated and five mildly decompensated patients. The average results are shown in chart 18. It can be seen that the two functions, ventilation and venous pressure, exhibited a rather remarkable parallelism. The lowest values at rest during and after exertion were obtained in the normal subjects and the highest values occurred in the decompensated persons, the compensated patients being intermediate. The degree of rise in both functions during exercise was greater in the patients than in the normal persons. After exertion the venous pressure of the normal subjects rapidly fell to below the original resting level, whereas the venous pressure of the decompensated patients remained elevated for several minutes and again the compensated patients had an intermediate curve.

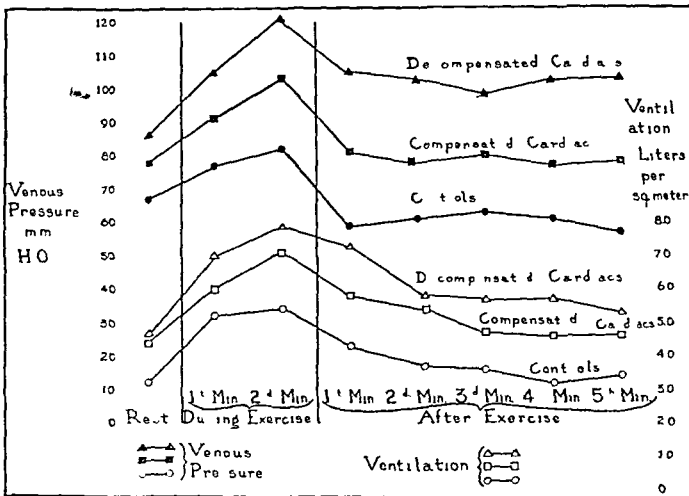


Chart 18—The hollow symbols denote ventilation, the black symbols, venous pressure. In the patients with cardiac decompensation (which was of mild degree) both functions were greater at rest, underwent greater increase during exertion and returned to normal more slowly than was the case in the normal controls. The compensated cardiac patients were intermediate. The parallelism between the two functions—venous pressure and ventilation—in any given group is rather striking.

These observations are in agreement with those of Schott, who noted that exertion caused a greater rise in venous pressure in patients with congestive failure than in persons with compensated cardiac disease or in normal persons. Since we have shown that a rise in venous pressure causes, *per se*, a reflex increase in the ventilation, it seems probable that these observations furnish the explanation for the fact that muscular exercise of this type (i.e., not sufficiently severe to alter the composition of the blood) results in a greater increase in ventilation in persons with cardiac disease than in normal subjects.

## COMMENT

The observations that have been presented seem to us to furnish a clear insight into the mechanism of the dyspnea that persons with cardiac disease feel on the performance of mild or moderate exertion.

First, the patient with heart disease has in most instances, some diminution of the vital capacity. This means that for any given level of ventilation he is more likely to feel respiratory distress than would be the case if his vital capacity were normal (Peabody, and Harrison, Tuiley, Jones and Calhoun). Furthermore, the decreased vital capacity usually causes, through vagal reflexes from the lungs, some increase in the ventilation even at rest (Harrison, Calhoun, Cullen, Wilkins and Pilcher). This brings about still further diminution in the respiratory reserve and brings the patient close to, or in more severe cases across, the

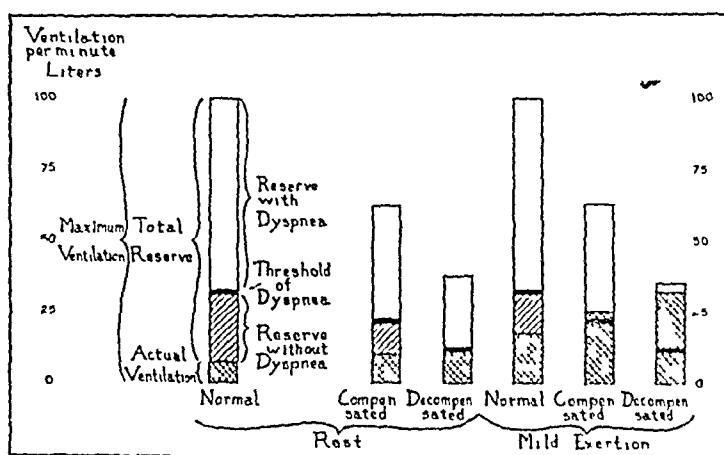


Chart 19—This is a diagram and does not represent actual data. The assumed vital capacities are 40, 25 and 15 liters for the normal subject, compensated patient and decompensated patient, respectively. It is assumed also that the maximum possible ventilation per minute is twenty-five times the vital capacity, and that dyspnea appears when the minute ventilation is one third or more of its maximum. It is seen that at rest the normal subject has a large respiratory reserve. Because of decreased vital capacity and increased ventilation the reserve is smaller in the compensated patient, whereas the decompensated patient is, even at rest, using all of his "asymptomatic reserve" and feels slightly short of breath. The latter patient suffers severe dyspnea on exertion because he has only his "symptomatic" reserve to call on. The compensated patient, who was comfortable at rest, being below the threshold of dyspnea, becomes slightly short of breath with exertion because he uses up all his "asymptomatic reserve" and a little of his "symptomatic reserve." Even during the exercise the normal subject has a large "asymptomatic reserve" and experiences no dyspnea. (It is assumed that the exercise is mild and only sufficient to increase the resting ventilation by 150 per cent in each instance.)

threshold of dyspnea, while in the resting state. These conditions are shown diagrammatically in chart 19.

When muscular exercise is performed, there is an immediate reflex increase in the ventilation of both the normal subject and the patient.



due to afferent impulses from the moving muscles. After exercise has continued for a short time there is a further increase in ventilation in both subjects, due to the rise in venous pressure which also causes reflex stimulation of the breathing. Since the venous pressure does not rise immediately but gradually, the ventilation is less during the first than during the subsequent minutes of the exercise. The person with cardiac disease has a greater rise in venous pressure and hence has a greater increase in ventilation than does the normal subject. Following the cessation of exercise the ventilation of the normal person decreases rapidly and approaches the resting level within two or three minutes. During this short period it remains somewhat elevated because of "hang-over" effects (i. e., chemical changes induced in the respiratory center by the previous stimulation). In the patient with cardiac disease there is not only this factor but also the additional one of continued stimulation from the rise in venous pressure which persists for several minutes after the exercise. Hence the ventilation of such patients returns to the resting level more slowly than does that of normal persons. The greater increase in breathing is likely to cause the ventilation to exceed the threshold of dyspnea, which is lower than in the normal subject because of the diminished vital capacity. Respiratory distress results. This series of events is shown in the right-hand portion of chart 19.

Throughout this paper we have emphasized the importance of the reflex control of respiration. This does not mean that we are unmindful of the importance of the chemical control. In severe exercise the blood undergoes chemical changes which may play a dominant rôle in altering the respiration. However, our interest has been centered on muscular exertion of the degree corresponding to that which is necessary in the normal life of patients. To them their disorder is of serious consequence only when it interferes with their daily tasks. Except in the case of laborers, the amount of muscular activity that is necessary to carry on a useful life is not associated with chemical changes in the blood. Cardiac disease becomes crippling to the average patient when dyspnea develops on walking on the level or up a slight grade. The exercise that we have studied corresponds to such efforts and the dyspnea is clearly of nervous origin, being due to reflex respiratory stimulation from the muscles, the heart, the lungs and possibly other sites as yet unknown.

#### SUMMARY

Observations have been made in patients with cardiac disease concerning the causes of dyspnea produced by mild exercise. It has been shown previously that exertion of this grade is not associated with alterations in the chemical composition of the blood. The following results have been obtained:

1 The vital capacity, which was lower than normal in our patients, did not usually undergo further significant reduction on muscular effort

2 The ventilation of patients with cardiac disease was greater at rest, rose more during exertion and remained elevated longer after exertion than was the case in normal subjects

3 During active movements of the hands the ventilation increased whether or not the circulation to the hands was obstructed by inflated blood pressure cuffs around the upper portions of the arms. The effect of passive movements was similar to that of active movements

4 In dogs passive movements of an extremity caused increased ventilation whether or not the circulation to and from the moving part was intact, but interference with the nerve supply of the moving part abolished the effect

5 In patients with cardiac disease the venous pressure was somewhat higher at rest, underwent greater rise during exertion and remained elevated longer than that of normal subjects. The latter group exhibited a prompt fall in venous pressure to or below the resting level immediately after the cessation of exertion

6 In dogs, raising the venous pressure either by infusions of fluid in the veins or by inflation of a balloon in the right auricle regularly caused an increase in ventilation so long as the vagus nerves were intact. When the vagi were cut, these procedures were usually without effect on the ventilation. Increasing the pressure in the great veins but not in the heart caused no effect on respiration, whether or not the vagi were intact

From these observations the following conclusions are drawn concerning the mechanism of the production, in persons with cardiac disease, of dyspnea on mild exertion

1 A decrease in vital capacity is important in two respects. (a) Per se, it lowers the respiratory reserve and thereby predisposes to dyspnea. (b) It increases the resting ventilation through vagal reflexes from the lungs and hence lowers the respiratory reserve still further

2 Afferent impulses from the moving muscles play a rôle in the production of dyspnea because they caused reflex increase of the ventilation during the exertion

3 Reflex stimulation of respiration, because of increased pressure in the right side of the heart and in cardiac ends of the great veins, is of especial importance. (a) In some cases venous pressure is higher than normal at rest and this increases the resting ventilation. (b) Venous pressure rises more than normally during exertion and hence the patient with cardiac disease has greater than normal ventilation during

exertion (c) The venous pressure, in contrast to its behavior in normal subjects remains elevated after exertion, and therefore the ventilation in patients with cardiac disease also remains elevated longer than normal after the cessation of exercise

4 All these factors so operate as to increase the value of the quotient  $\frac{\text{ventilation}}{\text{vital capacity}}$ , which is a measure of subjective respiratory distress in persons with cardiac disease

5 These data constitute additional evidence against the validity of the widely accepted but erroneous theory that the symptoms of cardiac failure are essentially and primarily due to a diminution in the minute output of the heart

# LIVER FUNCTION IN HYPERTHYROIDISM

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Jaundice is an unusual complication of exophthalmic goiter. Isolated cases have been reported from time to time, and have been collected by Sattler<sup>1</sup>. Assmann<sup>2</sup> has more recently reviewed the subject and added his experience.

Clinical evidence of disturbance of the liver in hyperthyroidism is offered by occasional cases with frank jaundice. In most instances, icterus is unrelated to the disease and is merely the result of an intercurrent complication, such as catarrhal jaundice,<sup>3</sup> cholelithiasis,<sup>4</sup> syphilis,<sup>5</sup> cholangitis or other infections.<sup>6</sup> Cardiac decompensation and associated factors<sup>7</sup> may account for the appearance of icterus in the terminal stages of exophthalmic goiter. (In two cases of terminal jaundice complicating thyrocardiac disease observed by me, the jaundice was explained on the basis of cholangitis demonstrated histologically.) Occasionally, however, the jaundice can be explained only as a direct

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1 Sattler, T. Basedowsche Krankheit, in Graefe-Saemisch Handbuch der gesamten Augenheilkunde, Leipzig, Wilhelm Engelmann, 1909, vol 9, pt 2, p 263.

2 Assmann, H. Leber und Milz bei Morbus Basedowni, München med Wchnschr **78** 221 (Feb 6) 1931.

3 (a) Eder, M. D. Three Cases of Jaundice Occurring in Persons Suffering from Exophthalmic Goiter, Lancet **1** 1758 (June 23) 1906 (cases 1 and 2). (b) Chvostek, F. Morbus Basedowni und die Hyperthyreosen, Berlin, Julius Springer, 1917.

4 Eder (footnote 3 a, case 3).

5 Habershon. Exophthalmic Goiter, Heart Disease, Jaundice, Death, Lancet **1** 510 (April 11) 1874. Gaill. Die Basedowsche Krankheit, München, 1883.

6 Chvostek (footnote 3 b). Mouriquand and Bouchut, cited by Assmann (footnote 2).

7 (a) Askanazy, M. Pathologisch-anatomische Beiträge zur Kenntnis des Morbus Basedowni, Deutsches Arch f klin Med **61** 118 (Sept) 1898. (b) Rautmann, H. Pathologisch-anatomische Untersuchungen über die Basedowsche Krankheit, Mitt a d Grenzgeb d Med u Chir **28** 489, 1915. (c) Assmann (footnote 2, 2 cases).

influence of the thyroid intoxication on the liver cells.<sup>8</sup> In fact, extreme instances occur in which the course is that of an acute yellow atrophy<sup>9</sup> of the liver. Assmann emphasized an associated toxic action on the kidney in some cases with resulting albuminuria, which is not dependent on cardiac failure. He has also observed the retreat of the icterus with improvement in the thyroid condition.

Hepatic lesions have been discovered at necropsy in some cases of hyperthyroidism. They vary from fatty changes<sup>10</sup> to a fully developed atrophic cirrhosis.<sup>11</sup> Weller<sup>12</sup> has described an "interlobular chronic parenchymatous hepatitis," characterized by lymphocytic infiltration, bile duct proliferation and increased stroma in the islands of Glisson, in 50 per cent of forty-four postmortem cases of exophthalmic goiter. A control group of patients of the same age and sex showed an incidence (30 per cent) of minor pathologic changes in the liver almost equal to that of the thyroid group. The thyroid intoxication may possibly render the liver more susceptible to unrelated toxic agents.

8 (a) Eger. Beitrag zur Pathologie des Morbus Basedowii, Deutsche med Wchnschr **6** 153, 1880. (b) Chvostek (footnote 3 b). (c) Pettavel, C. A. Weiterer Beitrag zur pathologischen Anatomie des Morbus Basedowii, Mitt a d Grenzgeb d Med u Chir **27** 694, 1914.

9 Barker, L. F. Thyreo-Intoxication with Necrosis and Atrophy of the Liver, Damage to the Heart Muscle and Kidneys, and Terminal Bronchopneumonia, M Clin North America **14** 261 (July) 1930. Hueck, cited by Assmann (footnote 2). Assmann (footnote 2). Raab, W., and Terplan, C. Morbus Basedowii mit subakuter Leberatrophy, Med Klin **19** 1142 (Aug 23) 1923. Kerr, W. J., and Rush, G. Y. Acute Yellow Atrophy Associated with Hyperthyroidism, M Clin North America **6** 445 (Sept) 1922.

10 Bodenstemei, F. Beitrag zur Kenntnis des Morbus Basedowii, Munich, Kastner & Lossen, 1901. Jacoud, cited by Assmann (footnote 2).

11 (a) Sattler (footnote 1). (b) Eger (footnote 8 a). (c) Farner, E. Beitrage zur pathologischen Anatomie des Morbus Basedowii mit besonderer Berücksichtigung der Struma, Virchows Arch f path Anat **143** 509 (March 9) 1896. (d) Mouriquand and Bouchut, cited by Assmann (footnote 2). (e) Paul, cited by Sattler (footnote 1). (f) Chvostek (footnote 3 b). (g) Askanazy (footnote 7 a). (h) Rautmann (footnote 7 b). (i) Landau. Pathological Histology of Basedow Struma, Munchen med Wchnschr **58** 1213 (May 30) 1911. (j) Neusser, cited by Sattler (footnote 1). (k) Marine, D., and Lenhart, C. H. Pathological Anatomy of Exophthalmic Goiter, Arch Int Med **8** 265 (Sept) 1911. (l) Hueck, cited by Assmann (footnote 2). (m) Assmann (footnote 2). (n) Pettavel (footnote 8 c). (o) Wegelin, C. Verhalten der ubrigen Organe beim Morbus Basedowii und den Hyperthyreosen Schilddruse, Henke, F., and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol 8, p 402. (p) Matti, Goodpasture and Holst, cited by Wegelin.

12 Weller, C. V. Hepatic Lesions Associated with Exophthalmic Goiter, Tr A Am Physicians **45** 71, 1930.

Experimental observations of the effect of thyroid substance or thyroxine on the liver have revealed a disappearance of glycogen<sup>13</sup> and fatty changes involving especially the center of the lobule of the liver<sup>14</sup>. No hepatic functional impairment, as measured by the dye excretion test, could be detected by Youmans and Warfield<sup>15</sup> in dogs that had been fed a large amount of thyroid extract. Pettavel<sup>8c</sup> and Wegelin<sup>110</sup> have noted livers absolutely devoid of glycogen in exophthalmic goiter.

Studies of hepatic function in hyperthyroidism have been based mainly on the results of the tetra-chlorphenolphthalein excretion test, the icterus index and sugar tolerance tests, with dextrose, galactose and levulose. Youmans and Warfield<sup>15</sup> found a retention of from 3 to 10 per cent of dye in the blood after sixty minutes in twenty-two of forty-eight cases and an elevated icterus index in seven of nine cases. Seven patients of the series were clinically jaundiced. However, their case notes indicate that in two of three fatal cases, with necropsy, a nutmeg liver due to chronic passive congestion existed, in the third case there was pneumonia, and in two nonfatal cases, auricular fibrillation. The results of the dye excretion test and the icterus index in these cases cannot be attributed to the hyperthyroidism.

Their studies in dextrose and levulose tolerance indicated a moderate degree of disturbance. They concluded, however, that there appeared to be no causal relationship between the degree of the liver damage and the disturbance in sugar tolerance. No correlation between the basal metabolic rate and functional impairment was apparent. There did seem to be some correlation between the loss of weight and the disturbance of liver function. This was interpreted as possibly due to the fact that in patients who had lost considerable weight an inability to maintain a satisfactory caloric intake developed.

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13 Cramer, W., and Krauss, R. A. Carbohydrate Metabolism in Its Relation to the Thyroid Gland, *Proc Roy Soc, London* **86B** 550 (June 10) 1913. Cramer, W. On the Glycogenic Function of the Liver and Its Endocrine Control, *Brit J Exper Path* **5** 128 (June) 1924. Parhon, M. Sur la teneur en glycogene du foie et des muscles chez les animaux traités par des preparations thyroïdiennes, *J de physiol et de path gen* **15** 75, 1913. Kuriyama, S. The Influence of Thyroid Feeding upon Carbohydrate Metabolism. I. The Storage and Mobilization of the Liver Glycogen in Thyroid Fed Animals, *J Biol Chem* **33** 193 (Jan) 1918, The Influence of Thyroid Feeding upon Carbohydrate Metabolism, *Am J Physiol* **43** 481 (July) 1917.

14 Farrant, R. Hyperthyroidism. Its Experimental Production in Animals, *Brit M J* **2** 1363 (Nov 22) 1913.

15 Youmans, J. B., and Warfield, I. M. Liver Injury in Thyrotoxicosis as Evidenced by Decreased Functional Efficiency, *Arch Int Med* **37** 1 (Jan) 1926.

In ten cases of exophthalmic goiter Kugelman obtained evidence of a disturbance of hepatic function by means of a levulose tolerance test<sup>16</sup> Alimentary galactosuria is often observed<sup>17</sup>

Adler and Lemmel<sup>18</sup> have noted abnormal cholesterol ester partition in a few cases of severe exophthalmic goiter The ester fraction was decreased as in cases of liver damage They attributed the fatty stools sometimes observed in this disease to a disturbed fat metabolism

The need for more sensitive methods of studying function of the liver cells has been stated repeatedly Recently,<sup>19</sup> I reported a new method of estimating such function based on the colorimetric estimation of the excretion in the urine of oxy-cinchophen (2-[orthohydroxy]-phenyl-quinoline-4-carboxylic acid), an intermediary metabolite of cinchophen metabolism In persons with normal function of the liver cells, less than 100 mg, or 21 per cent of the test dose, of cinchophen is excreted in this form With a disturbance of hepatic function, larger fractions are excreted The results of that study indicated that the disturbance in the metabolism of this choleretic substance might serve as a sensitive index of the function of liver cells The present study was made on a series of twenty consecutive cases of hyperthyroidism None of the patients, with the single exception of one with auricular fibrillation, gave any evidence of cardiac decompensation A definite functional disturbance of the liver has been demonstrated in most of these cases

#### METHODS EMPLOYED

The Brown modification of the Meulengracht method<sup>20</sup> was employed for the determination of the icterus index In my experience the range for normal readings by this method lies between 6 and 8, the zone for latent icterus lies between 8 and 20, and that for hypobilirubinemia, between 2 and 6

Urobilinuria was estimated by the zinc acetate method Excretion in normal persons, as determined by this method, in my experience does not exceed 20 mg daily

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16 Kugelman, B Ueber Storungen im Kohlhydratstoffwechsel beim Morbus Basedowii, *Klin Wchnschr* **9** 1532 (Aug 16) 1930

17 (a) Bauer, R Ueber die Assimilation von Galaktose und Milchzucker beim Gesunden und Kranken, *Wien med Wchnschr* **56** 201 (b) Strauss, H Leberfunktionsstorungen bei Morbus Basedowii, *Klin Wchnschr* **9** 2441 (Dec 27) 1930 (c) Hirose, M Ueber die alimentare Galaktosurie bei Leberkrankheiten und Neurosen, *Deutsche med Wchnschr* **38** 1414 (July 25) 1912

18 Adler, A, and Lemmel, H Zur feineren Diagnostik der Leberkrankheiten, *Deutsches Arch f klin Med* **158** 173 (Jan) 1928

19 Lichtman, S S Cinchophen Oxidation Test of the Function of the Hepatic Cells, *Arch Int Med* **48** 98 (July) 1931

20 Brown, A L A Rapid Clinical Method for the Determination of the Icterus Index, *Arch Path* **3** 409 (March) 1927

Urobilinogenuria was determined with Ehrlich's aldehyde reagent, the Wallace and Diamond<sup>21</sup> dilution method for quantitative results being employed. In normal persons, by this method a dilution of 1:20 or less is considered normal.

Galactose tolerance was determined according to Bauer.<sup>17a</sup> Forty grams of galactose (Merck) was administered in 400 cc of lemonade, and the urine was collected over a period of five hours. Sugar was estimated with Benedict's reagent, and a correction was made for copper reduction by galactose by multiplying by the factor 0.7. In normal persons, less than 3 Gm of galactose is excreted in the course of six hours following its ingestion.

The presence of tyrosine in the urine was determined by the tyrosinase method.<sup>22</sup>

The cinchophen oxidation test of function of the liver cells was carried out as described elsewhere.<sup>19</sup> The standard dose of 0.45 Gm of cinchophen was administered orally, and a quantitative fractional twenty-four hour specimen of urine was collected. The *o*-cinchophen content of each specimen was estimated colorimetrically by comparison with permanent standards prepared with a solution of 2- (orthohydroxy-phenyl) quinoline, 4-carboxylic acid (Calco). In persons with normal function of the liver cells, less than 100 mg, or 21 per cent of the test dose, is excreted in twenty-four hours in the form of *o*-cinchophen.

#### RESULTS

In the accompanying table are recorded the results of studies of the hepatic function and basal metabolic rates in a series of twenty cases of hyperthyroidism.

The icterus index was determined in seventeen cases. In three instances, increased readings, 10, 13 and 17, and 10, respectively, were obtained. In the second case, an encapsulated pleural effusion, with slight fever, possibly contributed to the latent icterus. In the other two cases no explanation of the latent icterus, other than the thyroid dysfunction, was evident. In six instances, hypobilirubinemia (icterus index, minus 6) was present.

Quantitative estimations of bilirubin by the van den Bergh method in eighteen cases failed to demonstrate an increased amount of bilirubin in the blood.

The galactose tolerance test, performed in sixteen cases, showed galactosuria in only three instances. In only one case, that of a diabetic patient with a glycosuria of 3.3 per cent preceding the test, was it excreted in abnormal amount (7.2 Gm). In the other two cases, 2.5 and 1.8 Gm, respectively, were excreted. These results agree with those of Assmann,<sup>2</sup> who obtained negative results with the galactose test in cases of exophthalmic goiter with jaundice.

Estimations of the urobilin in the urine were made in nine cases. Increased daily excretions as high as 150 mg, 26 mg and 115 mg,

21 Wallace, G. B., and Diamond, J. S. The Significance of Urobilinogen in the Urine as a Test for Liver Function, *Arch. Int. Med.* **35** (June) 1925.

22 Lichtman, S. S., and Sobotka, H. An Enzymatic Method for the Detection and Estimation of Tyrosine in Urine, *J. Biol. Chem.* **85** 261 (Dec.) 1929.



## Results of Liver Function Studies and Basal Metabolic Rate in Twenty Cases of Hyperthyroidism

Case	Loss of Weight per Cent. Time	Ic Index	Blood Bilirubin, Mg	Galac to suri	Uro bili ruria	Uro bilino genuria Dilution	Oxyphenol Excretion		Basal Metabolic Rate	Date of Test	Comments
							Mg	Per cent			
1 A J	3 6 mos	4 6	0.2 0.3	0	Traces	1.5 1.10	108 122 68 67 82 82	12.5 25.5 14.0 14.0 17 5	40 40 36 17 5	4/9 4/13  6/11 7/25 7/14	Compound solution of iodine 6/22, subtotal thyroidectomy 7/2
2 H W	15.5 8 mos	10 13	0.2	0		1.10	60.4 62.7 153 118 133 61	48 53 55  40 42	48 53 55	4/25 5/5 5/10  6/2 6/4	Hypertension compound solution of iodine 5/8, subtotal thyroidectomy 5/18
P M	11 7 wks	17	0.2	0	0 36		145  123 85 86	30.5  6.0 17.5 17.5	89 81 67 40 30	3/4 3/5 2/15 4/14 4/24	Encapsulated pleural effusion, subfebrile, compound solution of iodine 4/4, subtotal thyroidectomy 4/16
4 S S	20 4 mos	8 5	0.4				148 93	30.5 19.5	12 8	2/8 3/5	Compound solution of iodine 2/9 subtotal thyroidectomy 2/19
5 S L	0 1 yr	7	0.2	0	26		161 139 118 61	33.5 29.0 24.5 12.5	47 48 6 5	2/10 3/10 3/21 4/15	Auricular fibrillation, compound solution of iodine 2/11, subtotal thyroidectomy 4/6
6 J S	? 5 mos	6	0.2	2.5	115	Negative	202  112 157 87	42.0  23.5 33.0 18.0	53 17 3 20 37	2/10 2/14 2/24 3/10 3/22	Compound solution of iodine 2/11, subtotal thyroidectomy 2/26
7 F B	14 6 mos	4	0.2			Negative	167 157 132	35.0 33.0 27.5	23 25 5	4/23 4/29 5/2	Compound solution of iodine 4/29 subtotal thyroidectomy 5/7
8 E M	20 4 mos	3	0.2	0	Traces	Negative	56 50 54	11.5 10.5 11.0	39 46 3	4/24 5/4 5/27	Compound solution of iodine 4/25 subtotal thyroidectomy 5/7
9 R S	36 9 mos	4	0.2	0	0	Negative	133 70 83 78	27.5 14.5 17.0 16.0	36 26 10 6	3/30 4/14 4/21 5/5	Compound solution of iodine 4/8 subtotal thyroidectomy 4/23
10 M S	20 5 mos	10	0.3	0			127 189 126	26.0 39.0 26.0	34 30 52	12/12 12/23 1/15	Compound solution of iodine 12/9 subtotal thyroidectomy 12/26
11 P S	18 6 mos	6	0.2	0	Traces 0	1.5	145 123 102 63	30.5 25.5 21.0 13.0	27 17 5	5/1 5/11 5/24	Compound solution of iodine 5/5
12 J A	? ?	8	0.2				47 98	10.0 20.5	40 23	2/18 2/26	Hypertension
13 P R	15 1 yr	2	0.2	0			86 141	17.5 30.0	26 29	2/19 3/4	
14 M C	20 5 mos	4	0.2	0	Traces		75 67	16.0 14.0	50 50	3/14 3/19	Acute thyrotoxicosis, necropsy
15 S B	14 6 mos	4	0.2				215	45.0	46	11/29	
16 P B	20 1 yr		0.2	0			70	14.5	18 5	6/3 6/9	Compound solution of iodine 6/5
17 S S	7 9 wks	6	0.2	1.8			116	24.0	28	2/18	
18 B B	16.5 9 mos	7	0.2	0			104	21.5	36	12/11	
19 C M							110	23.0	21	6/11	Diabetes mellitus
20 P S	? ?			7.2	Traces		69 114	14.5 24.0	67 45	3/21 4/2	Diabetes mellitus compound solution of iodine 3/31

respectively, were encountered in three cases. The first case was that of the patient with latent icterus (icterus index, 17), a subfebrile temperature and pleural effusion, the second, that of a patient with auricular fibrillation. The remaining instance may possibly be attributed entirely to the thyroid disease.

In two cases (cases 6 and 15, table) urine was examined for tyrosine, and it was not found.

The cinchophen oxid test was carried out in every case. In sixteen of the twenty cases normal amounts of oxy-cinchophen were excreted in the urine in a twenty-four hour period. The largest excretions in the entire series were 5 mg (case 15), 202 mg (case 6) and 189 mg (case 10). The patient who excreted 202 mg had an attack of transient paroxysmal auricular fibrillation on the day of the test, which may have influenced the result. In the four cases (cases 8, 12, 14 and 16) with normal excretion of oxy-cinchophen, the results ranged between 50 and 75 mg. In nine of fifteen cases in which at least two estimations were made, the initial test made before treatment was instituted gave the highest excretion of oxy-cinchophen. In the five cases (cases 1, 4, 5, 9 and 11) in which the basal metabolic rate returned to normal after the administration of compound solution of iodine and after subtotal thyroidectomy or a period of rest, the excretion of oxy-cinchophen also dropped to normal. In four of seven cases (cases 2, 3, 6, 7, 10, 13 and 20) in which the basal metabolic rate remained elevated despite medical or surgical treatment, the excretion of oxy-cinchophen also remained elevated. In cases 2 and 3, in which the results of the cinchophen test became normal in spite of the elevated basal rates, reference to the table will indicate the atypical trend of excretion of oxy-cinchophen on repeated tests, and in case 3, the subfebrile course due to pleural effusion, which may be responsible for the persistently high metabolic rates.

In two cases (cases 19 and 20) of hyperthyroidism with diabetes mellitus 50 units of insulin was being administered during the test. Elsewhere<sup>19</sup> I have noted that in normal persons insulin decreases the excretion of oxy-cinchophen.

#### COMMENT

The excretory function of the liver as measured by bilirubinemia, icterus index, urobilinuria or urobilinogenuria did not appear to be impaired appreciably in this series of cases. In only two instances was there a latent icterus, and in one instance increased urobilinuria could be attributed to hyperthyroidism. Six patients had hypobilirubinemia (icterus index, minus 6). The apparent discrepancy with the results reported by Youmans and Warfield probably lies in the selection of cases. There was no case of frank jaundice and only a single case





# BRANCH ARBORIZATION AND COMPLETE HEART BLOCK

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The mode of cardiac conduction has passed through a prolonged controversial siege, but has emerged as a proven entity. The bundle of His, formerly considered as a passive agent, has now been shown to be actively engaged in generating and discharging the impulses which result in ventricular contraction (Ishihara and Nomura<sup>1</sup>). Instrumental in formulating these conclusions has been the advent of the electrocardiograph. In animals, severance of the common bundle or one of its main branches has yielded specific tracings, but its application in man is still a matter of dispute.

## NORMAL CONSIDERATIONS

Graphically, figure 1 shows what is now considered the normal course of impulses through the heart. From the sino-auricular node, situated at the junction of the superior vena cava and the appendage of the right auricle, fibers lead to the superior vena cava (Wenckebach's bundle), to the inferior vena cava by way of the linea terminalis (Thorel's bundle) and to the auricular musculature. (A direct communication between the sino-auricular and the atrioventricular nodes has not been fully established, although Thorel<sup>2</sup> and Nomura and Ida<sup>3</sup> have described an indirect communication by way of the inferior vena cava and the coronary sinus.) At the base of the auricular septum, opposite the coronary sinus, lies the atrioventricular node, which collects fibers from the coronary sinus and the walls of the left and right auricles. The common bundle of His originates at this point and runs in the membranous portion of the intraventricular septum. The bundle divides at the anterior border of this membrane a little in front of the anterior attachment of the septal segment of the tricuspid valve. The left

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Submitted for publication, May 12, 1932

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1 Ishihara, M., and Nomura, S., quoted by Orr, J. Oxford Medicine, New York, Oxford University Press, 1925, vol. 2, pt. 1, p. 371

2 Thorel, C. Ueber die supraventrikularen Abschnitte des sogenannten Reizleitungssystem, Verhandl. d. deutsch. path. Gesellsch. **14**, 71, 1910

3 Nomura, S., and Ida, H. Histologic Researches on Connection Between Sinoauricular and Tawara's Node, Taiwan Igakkai Zasshi **283**, 68, 1928

division perforates the muscular wall at the upper border of the muscular septum beneath the union of the right and posterior leaflet of the aortic valve. Beneath the endocardium the left bundle divides into an anterior, medial and posterior branch. (Kung<sup>4</sup>) Finer divisions are extensive and after sending branches to each of the papillary muscles of the mitral valve, the bundle breaks up into its arborizations.

The right division soon becomes subendocardial, courses downward to the moderator band and proceeds directly to the papillary muscle of the tricuspid valve, where it breaks up into its arborizations (Hill<sup>5</sup> and Lewis<sup>6</sup>). These arborizations communicate with the ventricular

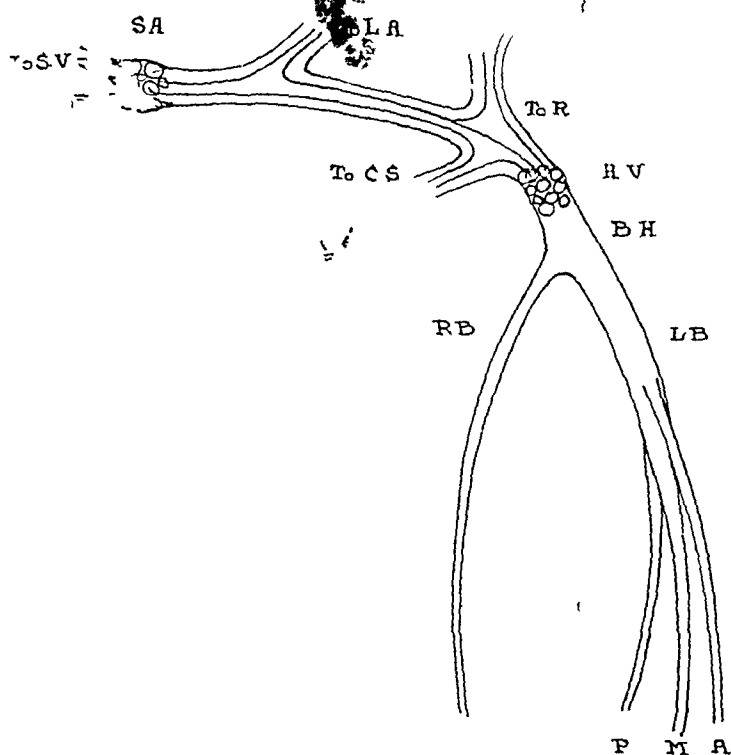


Fig 1—Schematic drawing of the entire conductive apparatus of the heart (Modified after Kunz and Mobitz). SA indicates sino-auricular node, AV, atrioventricular node, BH, bundle of His, RB, right branch, LB, left branch, (P, posterior, M, medial, A, anterior divisions), To SV, to the superior vena cava, To RA, to the right auricle, To LA, to the left auricle, and To CS, to the coronary sinus.

musculature by the subendocardial network of the Purkinje fibers (Lewis<sup>6</sup>).

4 Kung, S. K. Herzbloekstudien, über die normalen Histologie des Reizleitungssystems und pathologisch-histologische Befunde an blockierten Herzen des Menschen, Arch f exper Path u Pharmacol **155** 295, 1930.

5 Hill, I. G. W. Bundle Branch Block, Quart J Med **23** 15, 1930.

6 Lewis, T. Clinical Disorders of the Heart Beat, London, Shaw & Sons, Ltd, 1925, The Mechanism and Graphic Registration of the Heart Beat, London, Shaw & Sons, Ltd, 1924.

Communications have been demonstrated between both auricles (Bachmann<sup>7</sup>) and both ventricles (Wahlin.<sup>8</sup>)

# BUNDLE BRANCH BLOCK

When one of the other divisions of the bundle of His is interrupted, the impulse is conducted to the opposite ventricle not through the normal channel, but through the musculature which unites the chambers (Lewis). Experimentally, severance of the right branch of the bundle will be designated in the electrocardiographic tracing as a right bundle branch block. It is tall, broad and notched R, followed by a deep and wide S. In T, lead III small summit R, followed by a broad notched extensive dip S and then a large rounded elevation T. Likewise, interruption of the left branch will be noted graphically as a dextrocardiogram (roughly the antithesis of a levocardiogram). The foregoing findings, originally described by Eppinger and Rothberger,<sup>9</sup> have been verified by Winterberg, Lewis,<sup>6</sup> Wilson and Herrmann,<sup>10</sup> Smith<sup>11</sup> and Eppinger and Stoerk.<sup>12</sup> Both dogs and monkeys were used in the experiments.

This overwhelming evidence questions the interpretations of Wilson, MacLeod and Barker,<sup>13</sup> who found that by applying the exploring electrode to the heart (over gauze soaked in a warm saline solution) severance of the left bundle gave a levocardiogram and lesions of the right bundle, a dextrocardiogram. This possibility was first suggested by G. Fahr<sup>14</sup> and later by Wilson, who worked on exposed human

7 Bachmann, G. The Interauricular Time Interval, *Am J Physiol* **41** 309, 1916

8 Wahlin, B. Direct Connection Between Purkinje's Network of Filaments of Both Ventricles Through Interventricular Septum, *Upsala Lakaref orh* **34** 769, 1928

9 Eppinger, H., and Rothberger, J. Ueber die Folgen der Durchschneidung des Tawaraschen Schenkel des Reizleitungssystems, *Ztschr f klin Med* **70** 1, 1910

10 Wilson, F. N., and Herrmann, G. R. Bundle Branch Block and Arborization Block, *Arch Int Med* **26** 153 (Aug) 1920, An Experimental Study of Incomplete Bundle Branch Block and of the Refractory Period of the Heart of the Dog, *Heart* **8** 229, 1921

11 Smith, F. M. Further Observations on Experimental Lesions of the Branches of the Auriculoventricular Bundle of the Dog, *Arch Int Med* **28** 453 (Oct) 1921. Smith, K. S. Coronary Thrombosis and Complete Heart Block, *Lancet* **1** 685, 1930

12 Eppinger, H., and Stoerk, O. Zur Klinik des Elektrokardiograms, *Ztschr f klin Med* **71** 157, 1910

13 Wilson, F. N., Macleod, A. G., and Barker, P. S. The Order of Ventricular Excitation in Human Bundle-Branch Block, *Am Heart J* **7** 305, 1932

14 Fahr, G. An Analysis of the Spread of the Excitation Wave in the Human Ventricle, *Arch Int Med* **25** 146 (Feb) 1920

hearts. They concluded that the levocardio-graph which is usually interpreted as a left ventricular preponderance, should be called a right ventricular preponderance and *conversa*. However, Oppenheimer and Stewart,<sup>15</sup> working under similar conditions, obtained opposite results. Furthermore, left ventricular hypertrophy by far outnumbers right ventricular hypertrophy, which corresponds to the relationship of levocardio-graphs to dextrocardio-graphs. It is of course of no occurrence in the autopsy room to verify levocardio-graphs in cases of aortic regurgitation and essential hypertension.

#### DISCUSSION

In five cases demonstrating lesions of the conducting apparatus, histologic studies were made of the entire circuit to determine the nature of the lesion. These were compared with their corresponding electrocardiographic tracings when available.

In case 1 the isolated lesion of the left branch of the bundle of His and its corresponding dextrocardio-graph can be compared to an experimental study, and they aid substantially in establishing the original concepts of Eppinger and Rothberger.<sup>9</sup>

The number of cases of bundle branch block in which the electrocardiographic tracings have corresponded to the histologic observations is insufficient. Eppinger and Stoerk,<sup>12</sup> Cohn and Lewis<sup>16</sup> and Kauf have found levocardio-graphs in lesions of the right branch. However, Oppenheimer and Pardee<sup>17</sup> described one case in which the lesion was opposite to that predicted by the tracings, and Cohn and Lewis<sup>16</sup> found no lesions in a clinical branch block. These negative results do not necessarily refute the results of the experimental studies, as complete studies of both branches were not made.

**CASE 1—History**—A strongly built colored man, aged 48, was "perfectly well" until five and one-half months before his death, when transient "fainting spells" suddenly developed. These were accompanied by a numbness of his hands and spots before his eyes. Nocturnal dyspnea was common. Five and one-half weeks before hospitalization, dyspnea and edema of the ankles set in.

On further questioning, he said that he had had precordial pain, which radiated to the right lower quadrant, a hard cough and a loss in weight of 20 pounds (9 Kg.)

15 Oppenheimer, B. S., and Stewart, H. J. Dependence of the Form of the Electro-Cardiogram upon the Site of Mechanical Stimulation of the Human Ventricles, *J. Clin. Investigation* **3** 593, 1927.

16 Cohn, A. E., and Lewis, T. A Description of a Case of Complete Heart-Block, Including the Post-Mortem Examination, *Heart* **4** 7, 1912-1913, The Pathology of Bundle Lesions of the Heart, *Proc. New York Path. Soc.* **14** 207, 1914.

17 Oppenheimer, B. S., and Pardee, H. E. B. Site of the Cardiac Lesion in Two Instances of Intraventricular Heart-Block, *J. A. M. A.* **74** 1794 (June 26) 1920.



He had had rheumatism in 1914, which kept him in bed for eight weeks. A painful left knee had persisted. He said that he had not had chancres, but that he had had gonorrhea in 1896.

*Examination*—On physical examination his pulse was found to be irregular, with a rate of 56 per minute, the respiratory rate was 26, and the blood pressure was 150 systolic and 90 diastolic.

His pupils were equal and regular, but reacted sluggishly to light. Both carotids and subclavian arteries were palpable but not visibly.

The heart was enlarged downward and to the left, giving an aortic configuration. There was a double murmur over the aortic area, which was of a soft and blowing character.

The Kahn reaction of the blood was 2 plus. Urinalysis and chemical analysis of the blood gave negative results. An x-ray picture of the chest verified the enlarged heart and aortic configuration.

The electrocardiogram tracing was interpreted as follows (Dr. H. J. Isaacs): ventricular rate, 45, auricular rate, 90, left bundle branch block, partial heart block (2:1), one ventricular extrasystole (lead I, fig. 2c).

The diagnosis was syphilitic aortitis with insufficiency and heart block.

*Course*—While the patient was in the hospital, his radial pulse varied from 36 to 56 per minute. It was of good volume and was regular. His dyspnea, as well as his cough, continued, but syncope did not appear. Gradually, he became more dyspneic, his pulse became weak and thready, and finally, restlessness, a cold and clammy skin and fear of approaching death were present. His pulse rate preceding death was 44 per minute.

*Postmortem Examination* (Dr. R. H. Jaffe)—The body, weighing 170 pounds (77.1 Kg.) and being 188 cm. in length, was that of a tall, strongly built colored man whose oral mucosa was purple gray.

The heart (fig. 3) weighed 580 Gm. The epicardium was smooth and shiny. The transverse sinus was distended and filled with blood. The apex was formed by the left ventricle. The wall of the left ventricle measured 18 mm. in thickness, while that of the right was 8 mm. The myocardium was light purple brown and friable. The right leaflet of the aortic valve was diffusely thickened, especially in its medial and lower portion. The commissure with the left leaflet was thickened, greatly deformed and grayish white. The sinus of Valsalva of the right leaflet was transformed into a large sac, which extended into the ventricular septum. This sac measured 42 mm. in its transverse and 35 mm. in its vertical diameter. The wall, which separated the sac from the ventricular lumen, was composed of a firm light yellowish-gray tissue. This tissue fused with the aortic leaflet. The inside of the sac was lined by a grayish-white, firm, adherent membrane. In the lower third of the sac was an irregular opening with shaggy edges, 14 by 11 mm. in diameter, which connected the lumen of the sac with the left ventricle. The endocardium over the septum adjacent to the sac was thickened and yellow white.

The aorta measured 75 mm. (1 cm. above the aortic cusps). In the arch there were small grayish-white areas with irregular wrinkling and puckering. In the ascending and descending portions the intima was smooth except for a few calcific plaques.

The coronary arteries were thin-walled and had smooth intimas, except for an occasional yellow plaque up to 4 mm.

The remaining organs showed evidence of passive congestion.

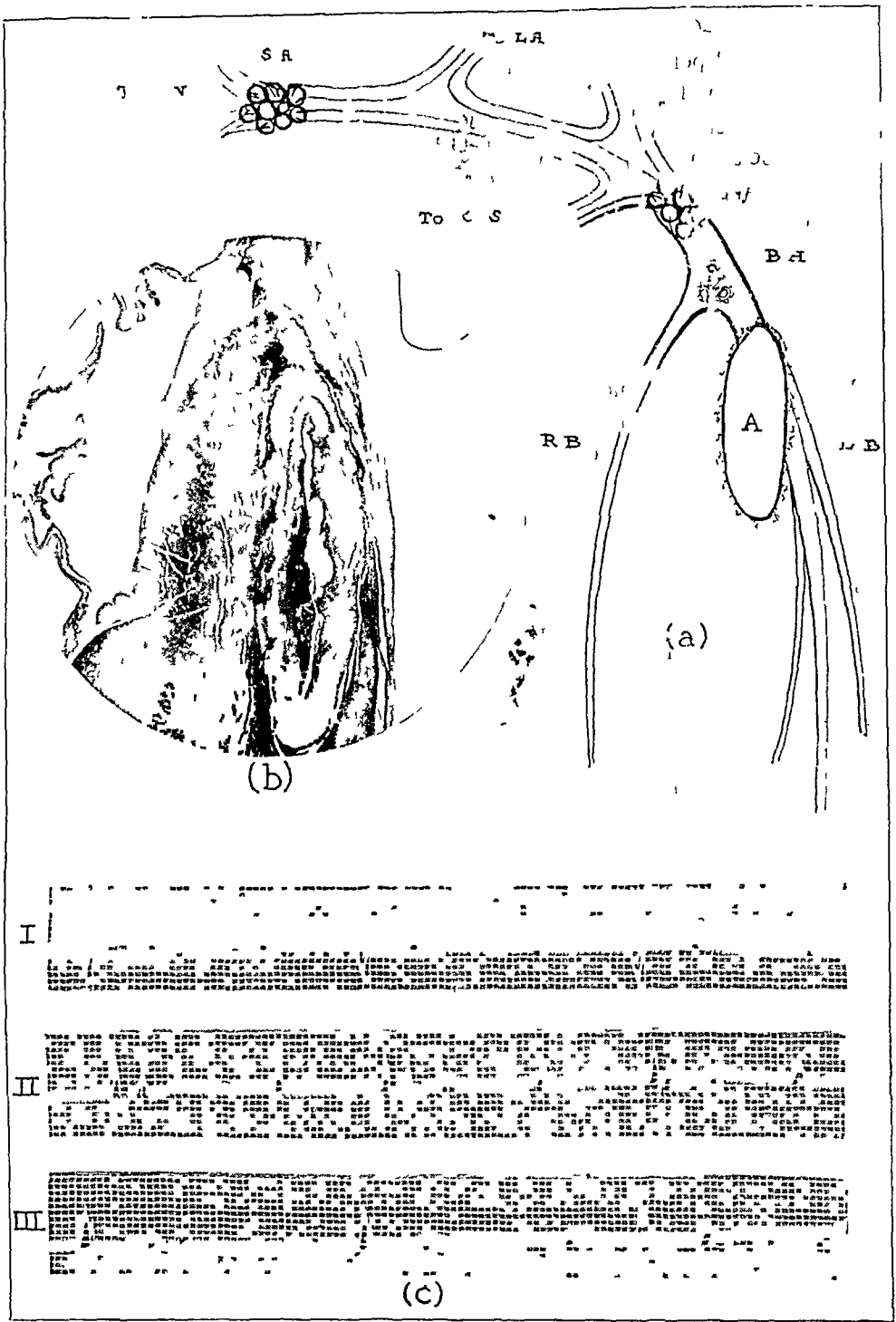


Fig 2—In *a* is a schematic drawing showing the interruption of the left branch of the bundle of His by the aneurysmal sac (*A*) *b* is a photomicrograph showing the same (reduced from  $\times 6$ ) *c* shows electrocardiographic tracings (three leads, showing a 2:1 heart block and a left bundle branch block)

*Microscopic Data*—Intraventricular Septum, Including the Posterior Aspect of the Right Auricle (fig 2, *a* and *b*). The aneurysm, described grossly, extended into the septum, and occupied the left half, while the right half appeared well preserved. The upper limit of the sac was 2 mm below the bundle of His, and it extended downward for a distance of 10 mm. Over this extent the left wall of the sac interrupted the left bundle save for a few strands. The remaining fibers of the left branch of the bundle were loosened, broken up in places and



Fig 3—Aneurysm of the right sinus of Valsalva rupturing into the left ventricle

infiltrated by lymphoid round cells and plasma cells. The cavity was lined by a membrane 2 mm in thickness, the outer aspect of which was composed of dense connective tissue with long fusiform cells which often contained fine, light brown pigment granules. The inner aspect was lined by a layer of hyalinized fibrin with histiocytic elements and small round cells. About the wall of the aneurysm was a dense infiltration by small round cells, plasma cells and histiocytes, filled with a light brown pigment.

The right branch of the bundle was separated from the sac by a 3 mm layer of muscle the fibers of which were moderately hypertrophic, and there was no interruption of their continuity or round cell infiltration. The right branch proper was well preserved. In the region of the bundle of His, there were small arteries which showed a distinct thickening of their walls as a result of intimal proliferation, in some instances obliterating the lumens. Their intima and periadventitia were infiltrated by small round cells. In the region of the sino-auricular and the atrioventricular nodes and the posterior wall of the right auricle no abnormal changes were seen.

Aorta. The adventitia was thickened by an increase in fibrous tissue and accumulations of round cells. The internal elastic laminae were thickened and were surrounded by lymphoid round cells and plasma cells. The entire extent of the media was penetrated by numerous young capillaries with round cell cuffs. There was marked scarring of the media about the capillaries or independent of them. The intima was thickened and presented hyaline plaques.

TABLE 1—Summary of Case 1

Pathologic		Diagnosis	Clinical	Electrocardiographic
Sino auricular node	No change	Syphilitic aortitis with insufficiency and part block		Left bundle branch block, partial heart block (2:1)
Auricular fibrils	No change			
Atrioventricular node	No change			
Common bundle of His	Marked perivascular round cell infiltration with endarteritis			
Left branch	Complete interruption by aneurysmal sac with marked round cell infiltration			
Right branch	No change			
Arborization	No change			
Comment		Kahn reaction of blood ++		

*Anatomic Diagnosis*—This was aneurysm of the right sinus of Valsalva of the aortic valve, extending into the interventricular septum and perforated into the left ventricle, interruption and compression of the left branch of the bundle of His by the aneurysm, eccentric hypertrophy of the heart, syphilitic aortitis, passive congestion of the lungs, liver, kidney and spleen.

The foregoing case is rare not only in its isolated affection of the left branch of the bundle of His, but also as a purely pathologic entity. Only five cases of aneurysm of the sinus of Valsalva have been reported (Castellano and Maldonado Allende,<sup>18</sup> Sheldon,<sup>19</sup> Marty and Froncin<sup>20</sup>

18 Castellano, T, and Maldonado Allende, I. Aneurysm of the Sinus of Valsalva and of the Thoracic Aorta Co-Existing with Syphilis of the Lungs, *Prensa méd argent* 17 346, 1930

19 Sheldon, J H. A Case of Aneurysm of a Sinus of Valsalva Bursting Externally, *Lancet* 1 178, 1926

20 Marty, P, and Froncin, J. Petit anéurisme du sinus de Valsalva demeure latent et rompu secondairement dans le péricarde, coexistence de lésion d'endocardite ulcéro-végétante, prédominant d'orifice aortique, *Bull et mém Soc méd d hôp de Paris* 94:580, 1924

and Roth<sup>21</sup>) In three cases the aneurysm extended outwards, and in two instances it ruptured into the pericardial sac, causing a heart tamponade and death Of Roth's two cases, in one the aneurysm compressed the interauricular septum, with a loss of conductivity of the bundle of His In the other, the lesion pressed on the atrioventricular node, but produced no microscopic changes in it John and Lewis<sup>16</sup> described an aneurysm originating from the posterior aspect of the left ventricle at the base of the heart, extending beneath the aortic valves into the interauricular septum The atrioventricular node was thus separated from the bundle of His Both branches were also affected by a fibrotic process Syphilis was the etiologic factor but the aorta showed only atherosclerotic changes Their patient was a white man, aged 46, who had a Stokes-Adams syndrome and a pulse rate of 30 per minute

#### ARBORIZATION BLOCK

Extensive subendocardial scarring involving the terminal branches of the bundle of His supposedly produces electrocardiographic tracings similar to those of bundle branch block except that the voltage is low This condition was termed arborization block by Oppenheimer and Rothschild<sup>22</sup> and was confirmed by Willius<sup>23</sup> Experimentally, it was not possible to produce such lesions by scarifying the entire endocardium Only by cutting one of the main stems of the bundle in addition to the scarification were graphs obtained similar to those described by Oppenheimer and Rothschild (Wilson and Herrmann,<sup>10</sup> Brinck, Miszke and Schone,<sup>24</sup> Rothberger and Winterberg,<sup>25</sup> Smith<sup>11</sup> and Master and Pardee<sup>26</sup>)

Coronary sclerosis with infarction and chronic myocarditis with scarring are the pathologic processes mentioned which will produce arborization blocks It is impossible to perceive that such lesions will

21 Roth, O Zur Kenntnis der Ueberleitungsstörungen des Herzens, *Deutsches Arch f klin Med* **112** 104, 1913

22 Oppenheimer, B S, and Rothschild, M A Abnormalities in the QRS Group of the Electrocardiogram Associated with Myocardial Involvement, *Proc Soc Exper Biol & Med* **14** 57, 1916, *Electrocardiographic Changes Associated with Myocardial Involvement*, *J A M A* **69** 429 (Aug 11) 1917

23 Willius, F A Arborization Block, *Arch Int Med* **23** 431 (April) 1919

24 Brinck, J, Miszke, B, and Schone, G Zur Klinik und Pathologie "des Arborisation Block" (Astblock), *Deutsches Arch f klin Med* **169** 129, 1930

25 Rothberger, C J, and Winterberg, H Ueber die Beziehungen der Herznerven zur atrio-ventrikulären Automatie, *Arch f d ges Physiol* **135** 559, 1910, *Experimentelle Beiträge zur Kenntnis der Reizleitungsstörungen in den Kammern des Säugetierherzens*, *Ztschr f d ges exper Med* **5** 264, 1917

26 Master, A W, and Pardee, H E B The Effect of Heart Muscle Disease on the Electrocardiogram, *Arch Int Med* **37** 42 (Jan) 1926

affect the subendocardial layer. Usually the myocardium generally is involved, including the bundle branches. One finds diffuse thickening of the subendocardial region with only slight changes in the myocardium in cases of long-standing dilatation of the heart (rickets, prolonged thyrotoxicosis and dilative diseases). In none of the foregoing instances were arborization blocks noted.

The explanation of the electrocardiographic tracings in the so-called arborization block is as follows. The widening and notching of the Q-R-S complex are a result of a branch lesion, while the low voltage is the result of the severe myocardial damage also affecting the arborizations. The bases for these conclusions are shown in case 2, in which a coronary sclerosis had produced a complete fibrous interruption of the right branch and, to a great extent, the left branch. A more recent coronary thrombosis had caused a complete infarction of the myocardium of the interventricular septum, also affecting the arborizations (fig 4).

**CASE 2—History**—A white man, aged 54, an American, was in fair health until two weeks before his death, when, while lying in bed, he fainted. The attack was momentary, but recurred a few hours later. He was brought to the hospital fully recovered and alert. On questioning, he said that he had not had any previous attacks, but that he had had hicups, nausea and vomiting for the day preceding the syncope. At no time did he experience precordial or epigastric distress. During the past year he had noticed numbness in his toes associated with a dull boring to burning pain. This was most marked on exertion, but at best was not alarming.

**Examination**—On physical examination, the patient was found to be slightly dyspneic, but he did not appear acutely ill. His temperature was 99.4 F, the pulse rate was 100 per minute, the respiratory rate, 24 per minute, and the blood pressure, 100 systolic and 70 diastolic.

The findings generally were not startling. There were moist râles in the base of the right lung posteriorly. The heart was not enlarged, the tones were equal and regular, but of only fair volume. The liver was enlarged and extended 4 cm beneath the right costal margin.

The extremities were numb and cold, and pulsations of the dorsal pedis artery were absent. There was no edema of the ankles.

The Kahn reaction of the blood was negative, the white blood count was 12,200, the urine was normal.

The electrocardiographic tracing was interpreted as follows (Dr H. J. Isaacs): rate, 125, somatic tremor, low voltage and notching of Q-R-S complexes, myocardial degeneration, T1 positive and T2 iso-electric, bundle branch lesion suggested, perhaps due to coronary disease—arborization block (fig 4c).

The diagnosis was coronary thrombosis with a secondary bundle branch lesion and arborization block.

**Course**—While the patient was in the hospital, he had frequent liquid, bloody stools, but he did not complain of pain. Singultus continued day and night. His pulse rate varied from 95 to 120 per minute, it was of fair volume and regular. Terminally, marked dyspnea, cyanosis and profuse diaphoresis developed.

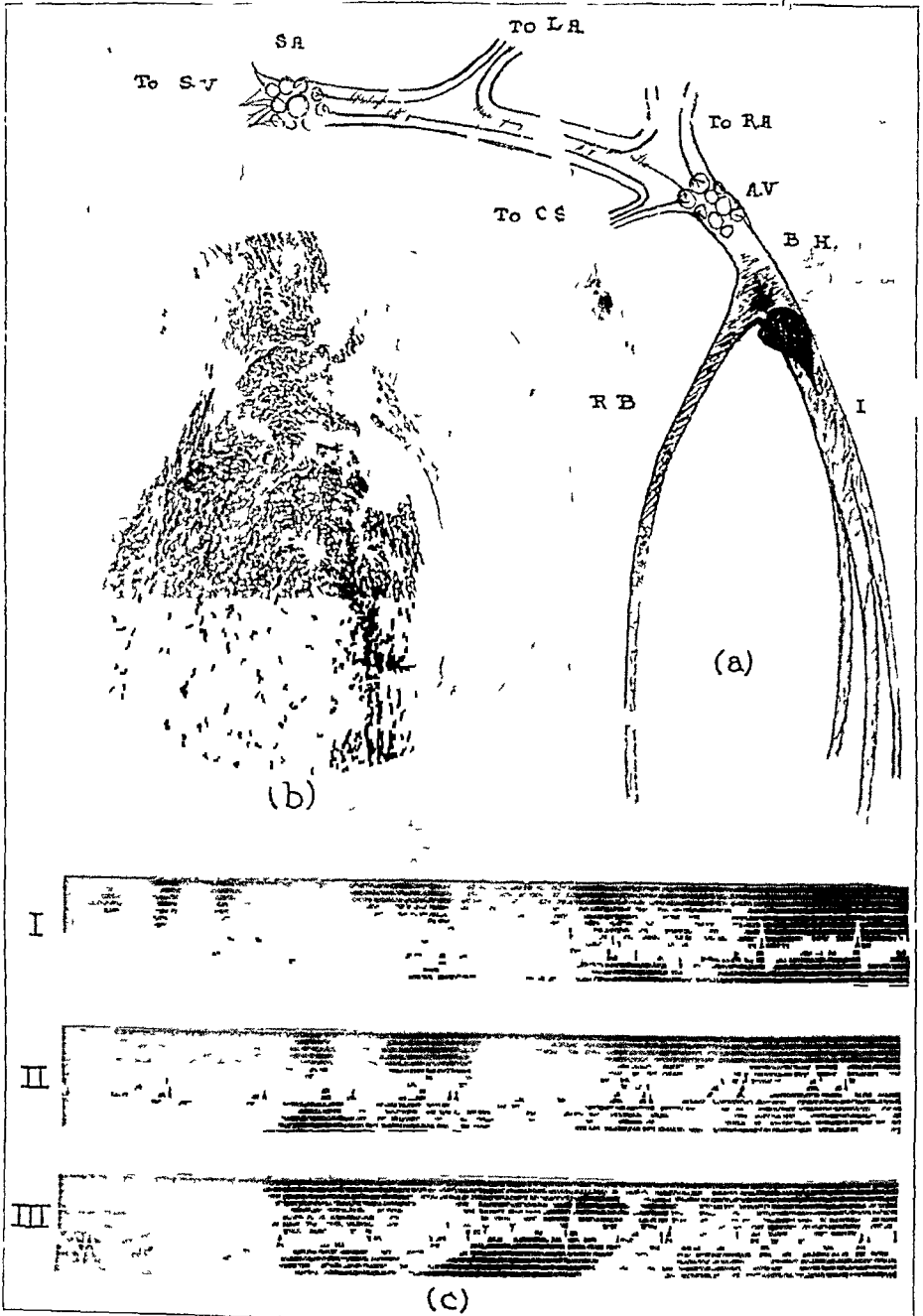


Fig 4—In *a*, the dark shading represents fibrosis which has interrupted the right branch of the bundle of His, and also the left branch except for a few fibers. The light shading represents necrosis of the smaller divisions of both branches. *b* is a photomicrograph in the region of the bifurcation of the bundle of His (reduced from  $\times 30$ ). Note the single muscle fibers extending about the outer aspect of the dense fibrotic area. These fibers were evidently sufficient to transmit impulses along the left branch. *c* is an electrocardiographic tracing showing low voltage and a notching of the Q-R-S complexes. Thus the diagnosis of an arborization block and a bundle branch lesion was made.

*Postmortal Examination* (Dr. S. R. Jesenthal) —The body, weighing 140 pounds (63 kg) and being 167 cm in length, was that of a strongly built white man, the skin of the neck and chest was discolored a deep purple.

The pericardial sac contained 100 cc of a reddish-brown fluid. The epicardium was injected and covered by a fine, fibrinous exudate.

The heart weighed 30 Gm. The left ventricular wall measured 13 mm, and the right ventricular wall, 3 mm. The myocardium was light brown, extremely soft and friable. At the apex of the left ventricle the wall was suddenly reduced to 1 mm, as the myocardium had lost its normal structure. It was very soft. In an area 1 cm in diameter on the anterior aspect of the left ventricle, only the thickened epicardium remained. The internal aspect of this infarcted site was lined by a reddish-gray, firmly adherent thrombus. The interventricular septum, beneath the membranous portion, for a distance of 5 cm in diameter, was transformed into a homogeneous, dry gray shrunken mass which extended through the entire wall and caused slight erosions of the epicardium of both ventricles.

TABLE 2—Summary of Case 2

		Findings	
	Pathologic	Clinical	Electrocardiographic
Sino auricular node	No change	Coronary thrombosis	Low voltage and notching of QRS complexes, myocardial degeneration, T1 positive and T2 iso electric, suspect bundle branch lesion perhaps due to coronary disease, arborization block.
Auricular fibrils	Moderate fibrosis		
Atrioventricular node	No change		
Common bundle of His	Moderate fibrosis with calcification		
Left branch	Marked fibrosis with interruption except for a few strands		
Right branch	Complete interruption by dense fibrous tissue		
Arborizations	Complete necrosis		

Both of the coronary arteries were tortuous and pipe-stemlike. The left one contained a small reddish-gray thrombus at its mouth which seemed to occlude the lumen completely. The right coronary artery was similar, except at its mouth, where a light yellowish-brown, atheromatous material seemed to obstruct it.

The aorta presented diffuse arteriosclerotic plaques up to 2 cm in diameter. In the abdominal portion, the lumen was almost completely occluded by a grayish-white thrombus which was moderately adherent to the wall. Beneath the thrombotic mass, the intima was studded by atherosclerotic ulcerations. The aortic thrombus extended into both iliac and femoral arteries, where it appeared well organized and practically occluded the lumens.

To account for the bloody stools, there was an annular area 3 cm wide at the sigmoid rectal junction, which was entirely necrotic and yellow green. A large vessel leading to this junction was occluded by a reddish-gray thrombus. The descending colon above this portion was the site of longitudinal ulceration up to 10 cm long and 1 cm wide.

*Microscopic Data*—Interventricular Septum Including the Posterior Wall of the Right Auricle (Fig 4a and b). The atrophic myocardium of the auricle was densely interspersed with broad fibrous tissue bands. In the region of the atrioventricular node were large elongated cells with round or oval nuclei and ample sarcoplasm. The sarcoplasm stained a yellow brown with the van Gieson method.



This accumulation of cells showed no abnormal changes, although surrounding it were small foci of calcification and fibrosis

Immediately beneath the membranous portion of the septum was a small, well isolated triangular area of muscle fibers that showed marked atrophic changes and interstitial fibrosis. This area was completely surrounded by dense fibrous tissue except for a few thin muscle strands that joined the subendocardial region of the left ventricle. The entire circuit stained a light yellow brown with the van Gieson stain. The continuity of the triangular area to the subendocardial region of the right ventricle was interrupted by dense fibrous tissue. The remaining septum showed a complete necrosis of the muscle fibers corresponding to the gross appearance.

*Anatomic Diagnosis*—This was Severe coronary sclerosis with thrombosis of the left coronary artery and atheromatous occlusion of the right coronary artery, myomalacia of the wall of the left ventricle and in ventricular septum, enlargement of the right branch of the bundle of His by dense fibrous connective tissue, interruption of the left bundle of His by dense fibrous tissue except for a few fibers, which were intact; recent serofibrinous pericarditis, severe atherosclerosis of the aorta with thrombotic occlusion of the entire abdominal portion and of both iliac and femoral arteries, intimal thickening of a branch of the inferior mesenteric artery, with necrosis of a segment of the sigmoid colon and several ulcers above this point.

#### COMPLETE HEART BLOCK

Experimentally, as well as clinically, complete heart block may be produced in the following manner: by interference with the conducting tracts, namely, the atrioventricular node and the bundle of His or its branches, by vagus stimulation (the left vagus because its action is more direct to the atrioventricular node), and by the introduction of toxic substances into the blood stream (digitalis, muscarine, diphtheria toxin and other substances, Lewis<sup>16</sup>).

Interference with the conducting apparatus has been described, resulting from inflammatory, vascular, degenerative, neoplastic, traumatic or congenital causes. Very little has been written regarding the pathogenesis of heart block in essential hypertension. The following case demonstrates the end-results of a hypertensive heart in which the coronary arteries were grossly normal.

*CASE 3—History*—A white man, aged 70, had been in and out of the hospital several times during a two year period. He complained of precordial pain, dyspnea on exertion and edema of the ankles.

*Examination*—On physical examination he was found to be well nourished and developed and though comfortable, had a regular pulse rate of 36 per minute. His blood pressure was 182 systolic and 64 diastolic.

The heart was markedly enlarged, with the left border in the anterior axillary line. A soft systolic blow was heard at the apex. The tones were weak but regular and slow (36 per minute).

The lungs were normal except for fine moist râles in the bases.

The liver was tender and slightly enlarged.

The lower extremities and genitalia were markedly edematous.

The electrocardiographic report read as follows (Dr H J Isaacs) ventricular rate, 50, auricular rate, 90, left ventricular preponderance, marked myocardial degeneration, and a few ventricular extrasystoles. Lead II showed evidence of a complete heart block (fig 5c)

The diagnosis was hypertensive heart with decompensation and complete block

*Course*—The patient was digitalized and quickly improved. He left the hospital only to return shortly afterward with cardiac decompensation. These measures were repeated several times. Finally, he entered the hospital with similar complaints one month before his death. His heart rate varied from 40 to 48 per minute. The electrocardiographic tracings were unchanged.

Decompensation was severe, with râles in the bases of both lungs, tenderness of the liver and marked dependent edema. The patient was cyanotic, his lungs were filled with loud bubbling râles, and he complained frequently of cardiac pain.

TABLE 3—Summary of Case 3

Pathologic		Diagnosis	Clinical	Electrocardiographic
Sinoauricular node			Hypertensive heart disease	Marked myocardial degeneration and complete heart block
Auricular nodis			with decompensation and heart failure	
Atrioventricular node				
Common bundle of His	Fibrous and fatty with calcific deposits			
Left branch	Completely interrupted by dense fibrous tissue and calcific deposits			
Right branch	Completely interrupted by dense fibrous tissue and calcific deposits			
Arborizations	Moderate subendothelial fibrosis of right and left ventricle			
Comment			Blood pressure 182 systolic and 64 diastolic (when decompensated)	

Venesection proved of no avail. In this state the patient died, two years after the first observation.

*Postmortem Examination* (Dr R H Jaffé)—The body, weighing 185 pounds (83.9 Kg) and being 171 cm in length, was that of a well nourished white man whose face was cyanotic and whose lower extremities and scrotum were markedly edematous.

The heart weighed 700 Gm. The epicardium over the lateral aspect of the left ventricle was slightly thickened, otherwise, it was smooth and shiny. The wall of the left ventricle measured 16 mm, while that of the right ventricle was 6 mm. The myocardium was a light purple brown, mottled with purple gray. Both chambers were dilated, the trabeculae carneae being flattened. The endocardium appeared unchanged.

The coronary vessels were thin-walled, and the intima of the circumflex branch of the right side contained single, small, light yellow plaques.

The spleen and the liver showed signs of long-standing passive congestion. There were no other important findings.

and no abnormal changes, although surrounding it and fibrosis

The membranous portion of the septum was a small, well defined area completely surrounded by dense fibrous tissue. The muscle fibers that showed marked atrophic changes and the triangular area to the subendocardial region of the septum stained a light yellow brown with the van Gieson. The remaining septum is composed of the muscle fibers corresponding to the gross

This was Severe coronary sclerosis with thrombosis of the atheromatous occlusion of the right coronary artery, left ventricular septum, and interventricular septum. The dense fibrous connective tissue, inter-tissue except for the fibers, severe atrophy

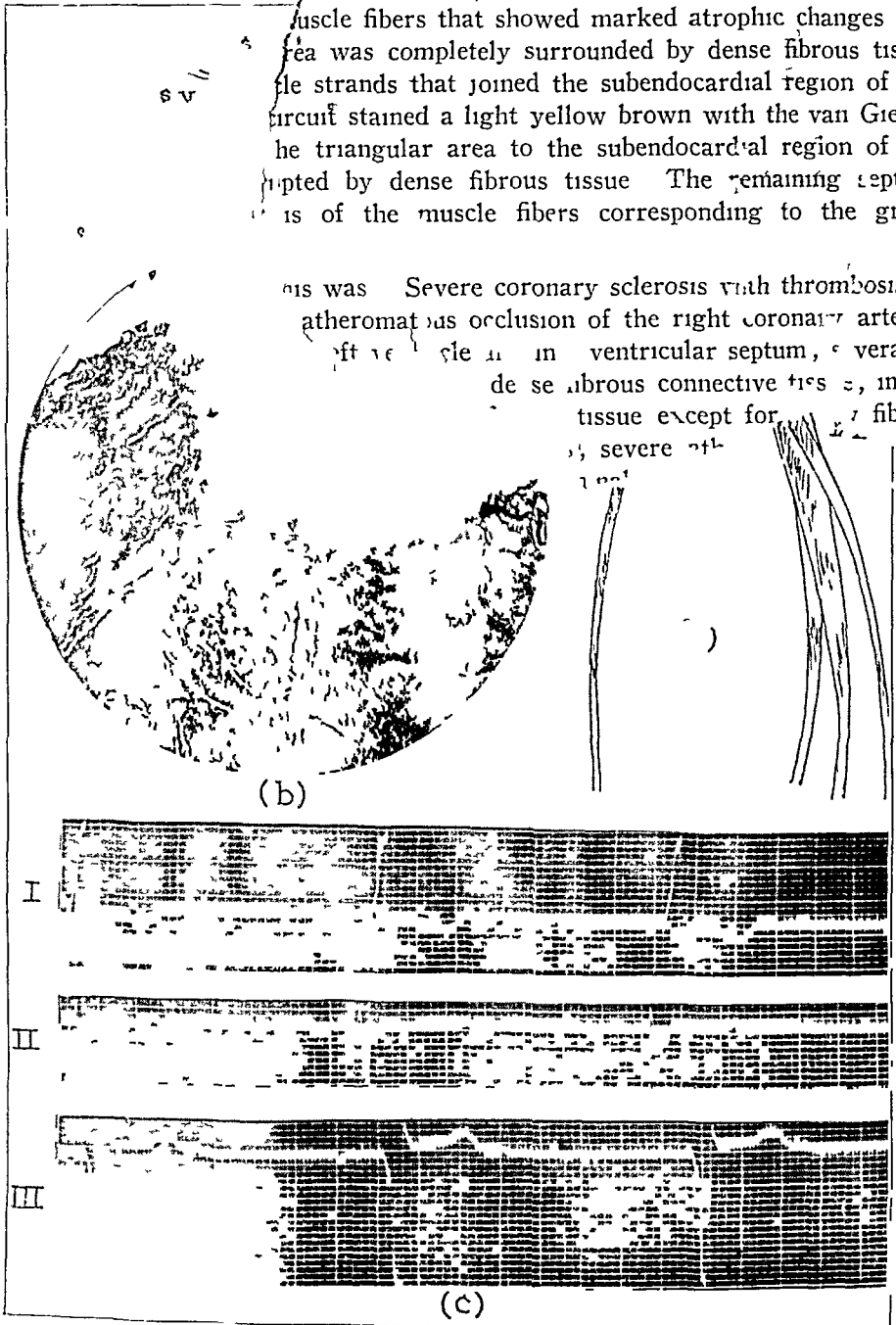


Fig 5—In *a* fibrosis, calcification and fatty changes affect the common bundle of His and both of its branches. *b* is a photomicrograph, showing the same. The fat cells are seen in the roughly triangular clear zone with faint subdivisions (reduced from  $\times 16$ ). *c* is an electrocardiographic tracing (three leads), showing evidence of a complete heart block in lead II. There is a left ventricular preponderance

The electrocardiographic report read as follows: essential pathologic changes were rate, 50, auricular rate, 90, left ventricular prepericardial septum with the membrane degeneration, and a few ventricular extrasystoles. Little complete heart block (fig 5c).

The diagnosis was hypertensive heart with decompensation composed of large fat cells.

*Course*—The patient was digitalized and quickly improved only to return shortly afterward with cardiac decompensation. From repeated several times. Finally, he entered the hospital on the right side, the muscle plants one month before his death. His heart rate was normal. The electrocardiographic tracings were unchanged.

Decompensation was severe, with râles in the bases of the lungs and marked dependent edema. The patient was filled with loud bubbling râles, and he complained

TABLE 3—S.

walls of the muscle fibers and elastic membranes were thickened, and the intimas were unchanged and the showed a thickening of their walls. The precapillaries were distended and filled with blood.	due to hypertrophy of internal and external arteries in many instances. The arterioles, similarly, capillaries were hugely
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Outside of the arteries the muscle fibers were hypertrophic, and a yellowish-brown pigment had accumulated about the nuclei.

*Anatomic Diagnosis*—This was complete fibrotic interruption of the bundle of His at the point of division, hypertrophy of the heart, especially the left ventricle, with marked dilatation of all the cardiac chambers, chronic passive congestion of the liver and spleen with fibrosis, ascites and anasarca of the lower extremities.

The enlarged heart (700 Gm) without evidence of valvular or coronary changes, the increased blood pressure, 182 systolic and 64 diastolic, and the absence of pathologic changes in the kidneys speak for an essential hypertension. The histologic changes in the arteries, arterioles and capillaries, especially of the heart, bear out this diagnosis.

The etiology of essential hypertension is unknown, but it is suggested that the underlying pathogenesis is an increased tonus of the small arteries and the arterioles produced by some toxin, bacterial, metabolic or chemical. The toxin, while producing an increased tonus of the small arteries and the arterioles, causes a dilatation of the precapillaries and capillaries (Ricker<sup>27</sup> and Dietrich<sup>28</sup>). From a histologic standpoint, this is borne out in case 3 by the hypertrophy of the media of the small arteries and arterioles and the dilatation of the precapillaries and capillaries.

27 Ricker, G. Sklerose und Hypertonie der innervierten Arterien, Berlin, Julius Springer, 1927.

28 Dietrich, A., and Nordmann, M. Versuche zur hamorrhagischen Diathese. Verhandl. d. deutsch. path. Gesellsch. 25: 46, 1930.

With increasing doses of the noxa, there are a greater constriction of the small arteries and arterioles and a wider dilatation of the pre-capillaries and capillaries, which may lead to paresis of the smaller vessels (prestasis), or actual paralysis (stasis) (Ricker<sup>27</sup>). With such vascular phenomena degenerative changes and even necrosis may result.

This vascular mechanism is apparently responsible for the pathologic changes described. As the picture is that of an advanced stage in which fatty, calcific and fibrotic changes are prominent, the changes embrace the bundle of His and its branches, because they are richly supplied with blood vessels.

#### INFLAMMATORY LESIONS OF THE CONDUCTIVE APPARATUS

The existence of myocarditis as an entity is much disputed. Undoubtedly, it exists. Inflammatory conditions of any organ may exist. Acute isolated myocarditis has been described by Monckeberg,<sup>29</sup> Schmincke,<sup>30</sup> de la Chapelle and Graef,<sup>31</sup> Scott and Saphir<sup>32</sup> and many others. The majority of the reports, however, exclude the valvular lesions merely by gross inspection. That microscopic lesions do exist has been shown clearly by de Vecchi.<sup>33</sup> Whether the endocardial affections precede or are concomitant with the myocardial involvement is sometimes difficult to determine, but the importance of these microscopic lesions should not be underestimated in the pathogenesis of myocarditis.

In case 4, an acute myocarditis was associated with micro-ulcerative endocarditis. Grossly, the valves appeared unchanged. It is possible that the endocarditis influenced the myocarditis. Unfortunately, an electrocardiographic record was not obtained in this case because the patient died shortly after entering the hospital. Although the slow pulse rate (from 30 to 40 per minute) does not necessarily spell heart block, it is interpreted as such because of the anatomic findings.

**CASE 4—History**—A white man, aged 42, was brought to the hospital markedly dyspneic, cyanotic and complaining of severe abdominal pain, he hiccuped

29 Monckeberg, J. G. Die Erkrankungen des Myokards und des spezifischen Muskelsystems, Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, pp. 356, 366, 387 and 435, Zur Einteilung und Anatomie des Adams-Stokes'schen Symptomenkomplexes, Beitr. z. path. Anat. u. z. allg. Path. **63**: 77, 1916, Das spezifische Muskelsystem in Mensch. Herzen, Ergebn. d. allg. Path. u. path. Anat. **19**: 328, 1921.

30 Schmincke, N. Isolierte akute, diffuse interstitielle Myokarditis, Deutsche med. Wchnschr. **47**: 1047, 1921.

31 de la Chapelle, C. E., and Graef, I. Acute Isolated Myocarditis, Arch. Int. Med. **47**: 942 (June) 1931.

32 Scott, R. W., and Saphir, O. Acute Isolated Myocarditis, Am. Heart J. **5**: 129, 1929.

33 de Vecchi, B. The Endocarditic Process in Childhood, Arch. Path. **12**: 49 (July) 1931.

at frequent intervals. His history was indefinite, he had had cramplike pains in his abdomen five days previously, following a gastric upset. The pains were less severe the following day, but recurred more severely and persisted. Vomiting, from three to four times daily, was associated with the pain, and a relative thought that it had been blood-tinged at one time. Together with the foregoing symptoms, dyspnea was marked.

The past history was irrelevant, the patient having enjoyed good health until the present illness.

*Examination*—On physical examination his temperature was found to be 103.8 F (rectal), the respiratory rate 32 per minute. The pulse was imperceptible at the wrist, but the carotids pulsated irregularly at a rate of from 30 to 40 per minute. The blood pressure could not be obtained.

The heart was slightly enlarged to the left, the apex being a little outside of the left nipple line. The tones were weak and muffled, and the rate was from

TABLE 1—Summary of Case

	Pathologic	Clinical	Electrocardiographic
Sino auricular node	No change	Coronary thrombosis	No tracing made as patient died 2 hours after entering hospital
Auricular fibrils	Few polymorphonuclear leukocytic infiltrations	with possible heart block or bleeding peptic ulcer	
Atrioventricular node	No change		
Common bundle of His	Acute inflammatory changes with hemorrhages		
Left branch	Destroyed by marked acute inflammatory changes and hemorrhages		
Right branch	Destroyed by moderate acute inflammatory changes and hemorrhages		
Arborizations	Slight granulocytic infiltrations and hemorrhages		
Comments	Micro ulcerative endocarditis of aortic valve	Heart rate from 30 to 40 per minute	

30 to 40 per minute. The lung findings were entirely negative. The abdomen was distended, but there were no masses, tenderness or rigidity. Borborygmus was increased throughout. The skin was cold and clammy, and the reflexes were diminished.

The impression was that the patient had coronary thrombosis with possible heart block, but because of the history of bleeding and abdominal cramps, a bleeding ulcer was considered.

Although the patient gave the major portion of the history, his death occurred two hours after he entered the ward, so that no further study was possible.

*Postmortem Examination* (Dr S. R. Rosenthal)—The body, weighing 142 pounds (64.4 Kg) and being 162 cm in length, was that of a strongly built Italian man, whose face was moderately cyanotic.

The heart weighed 325 Gm, the left ventricle measured 15 mm, and the right ventricle, 2 mm. The myocardium was a deep purple brown and soft. The valves appeared normal grossly. In the region of the membranous portion of the interventricular septum, facing the left ventricle, there was an irregular subendothelial

extravasation of blood, extending for a distance section of the interventricular septum reveal through the entire wall, for 1 cm below the

The coronary arteries were thin-walled, and by a yellow plaque of 2 or 3 mm. The intima of the aorta was smooth

The spleen weighed 140 Gm, its consistency was soft, and the pulp was purple red mottled with pink red

The remaining organs showed evidences of passive congestion. The gallbladder contained mulberry-shaped, light yellowish-green stones. The mucosa of the gallbladder was trabeculated and light yellow

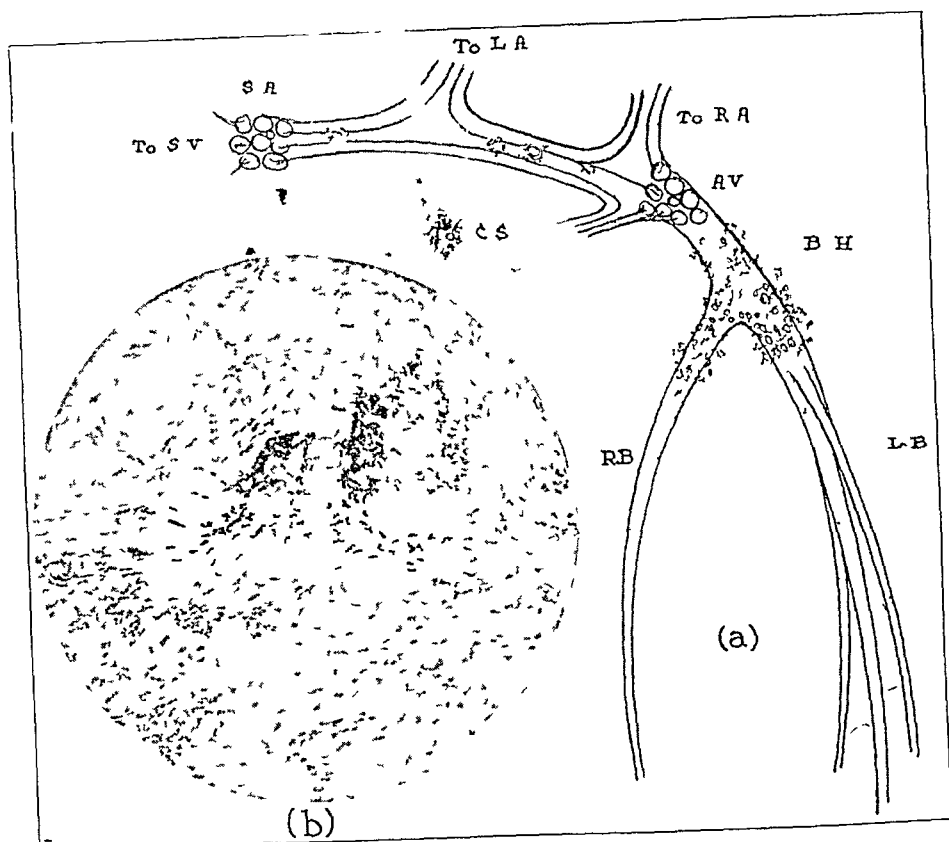


Fig 6—In *a* there are acute inflammatory exudate and hemorrhage in the region of the bundle of His. *b* is a photomicrograph in the region of the common bundle (reduced from  $\times 150$ )

*Microscopic Data* (fig 6a-b)—Interventricular Septum, Including the Posterior Aspect of the Right Auricle. Beginning in the lower third of the membranous portion of the septum on the right side and extending for 1 cm into the apex of the muscular portion of the septum were extensive extravasations of blood which permeated beneath the endocardium of the left ventricle, and to a lesser extent the right ventricle. Marked polymorphonuclear leukocytic infiltrations were found about the extravasated blood, and granulocytes invaded both branches of the bundle just beneath the bifurcation. In the remaining portion of the muscular septum, the muscle fibers were hypertrophic, their cross-striations were indistinct, and about the nuclei were moderate amounts of a golden yellow pigment. Occasionally a small lake of blood was found about the vessels, which were surrounded by round cells and granulocytes.

at frequent intervals. His small perivascular leukocytic infiltrations. The abdominal five days previous. The sino-auricular nodes appeared well preserved.

Aortic Valve.—The aortic surface of the valve was covered by a cellular exudate, which was composed of several distinct layers. The proximal layer presented a diffuse zone of necrosis in which polymorphonuclear leukocytes were found in different stages of degeneration. The distal aspect was covered by a cellular layer of granulocytes, mononuclear cells and swollen fibrocytes. This layer was covered by proliferated endothelium. The necrosis and leukocytic infiltrations extended down into the sinus of Valsalva, but the covering productive layer became less and less distinct. On the entricular aspect of the valve was also a thin layer of leukocytes and fibrin. In the fat tissue between the auricle and the root of the aorta were dense accumulations of polymorphonuclear leukocytes and mononuclear cells.

*Anatomic Diagnosis*.—This was acute micro-ulcerative suppurative endocarditis of the aortic valve and suppurative hemorrhagic interstitial myocarditis, involving especially the bundle of His, acute tumor of the spleen, passive congestion of the myocardium and the liver, cholecystitis and cholelithiasis.

Similar to acute myocarditis, the etiology of subacute myocarditis is unknown. Because of the absence of Aschoff nodules and gross valvular lesions, it is not considered rheumatic and is thought by some to be primarily a myocardial inflammation (Roque and Levy,<sup>34</sup> Monckeberg,<sup>29</sup> Kiehl<sup>35</sup> and Boikan<sup>36</sup>). Other authors believe that it is tuberculo-toxic (Massini<sup>37</sup>). The inadequate microscopic examinations of the heart valves again suggest them as possible sources of the infection.

The microscopic changes in the myocardium in case 5 are similar to those described in subacute myocarditis (Roque and Levy, Monckeberg and Kiehl) or myocarditis perniciosa (Boikan). This consists of a round cell and histiocytic infiltration which affects the ventricles more than the auricles and the interventricular septum more than the outer walls. No Aschoff nodules are present. Yet in case 5 a small, chronic, rheumatic lesion was found involving the posterior cusp of the mitral valve with a more recent verrucous deposit. It is possible to conceive that this lesion might have been microscopic in size, as in case 4, and overlooked grossly.

Case 5 represents a complete heart block as the result of a subacute inflammatory process involving the main bundle and both of its branches and a right ventricular preponderance as the result of a myomalacia of the apex of the left ventricle. The exudate also extended beneath the

34 Roque and Levy. Un cas de myocardite subaigue primitive, Arch d mal du cœur 7 10, 1914

35 Kiehl, L. Beitrag zur Kenntnis der idiopathischen Herzmuskelerkrankungen, Deutsches Arch f klin Med 48 414, 1891

36 Boikan, W. S. Myocarditis perniciosa, Virchows Arch f path Anat 282 46, 1931

37 Massini, R. Ueber tuberkulose Myokarditis, Schweiz med Wchnschr 51 1156, 1921



endocardium of both ventricles, thus involving the arborizations. Yet there was no arborization block clinically. The short duration of the disease was probably insufficient to destroy completely the terminal ramifications of the bundle of His.

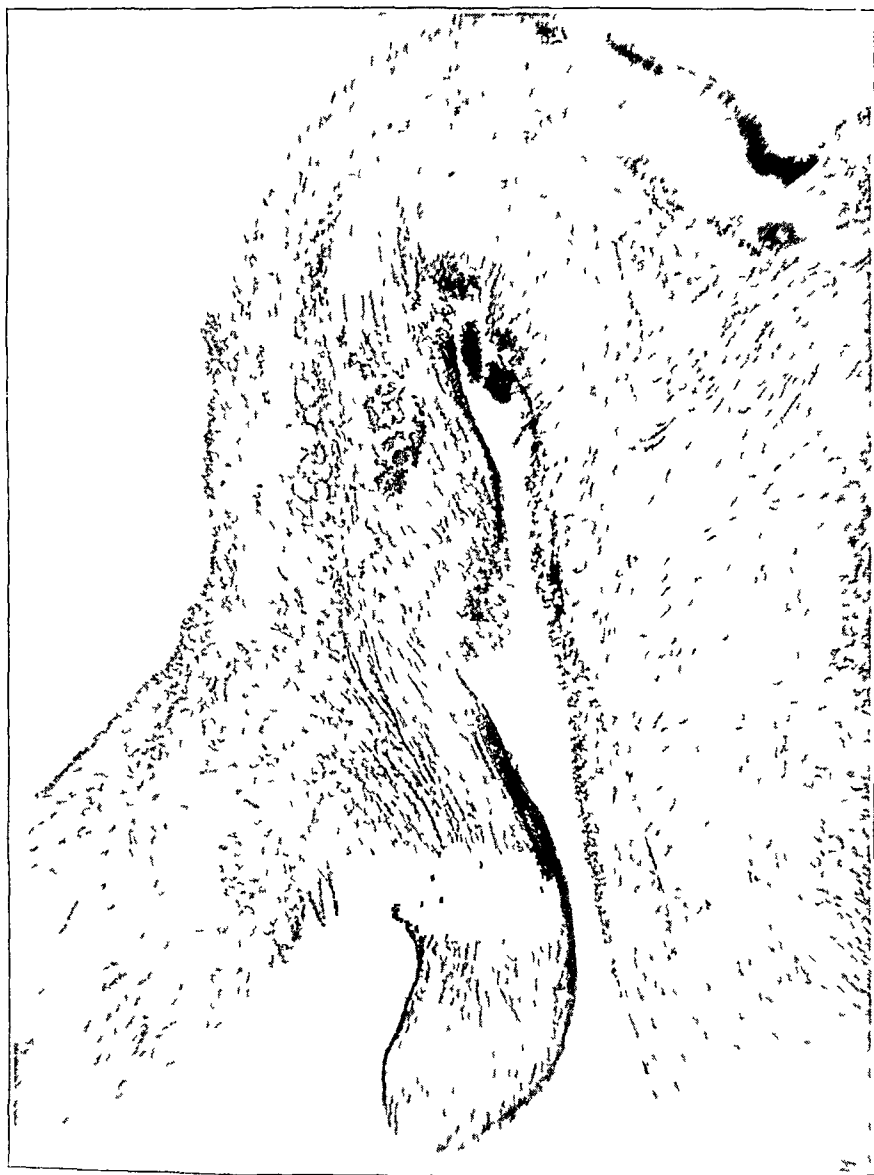


Fig 7—Micro-ulcerative endocarditis of the aortic valve (reduced from  $\times 45$ )

**CASE 5—History**—A white boy, aged 17 years, was well until four months before examination, when he began to experience epigastric fulness, which was not associated with meals and was not accompanied by nausea or vomiting. Soda or food did not relieve the distress. He had had numerous sore throats, and two months previously he had had a recurrence.

All of the foregoing symptoms were rather mild until four days before hospitalization, when the patient began to have chills and fever with marked diaphoresis. With rest he was slightly relieved, but on arising he became dizzy and weak and

had hot flashes. Three days following the onset, on getting out of bed, he fainted. Recovery was instantaneous. However, five and one-half hours later a convulsive seizure set in which recurred in two hours. He was rushed to the hospital, and in the interim had two more convulsions.

Previously, he had noticed sharp pains over his precordium, palpitation and dyspnea, but never convulsions. His previous illnesses included chickenpox, whooping cough and tonsillitis, as noted. Tonsillectomy, which was performed four years before hospitalization, did not abate the sore throats.

*Examination*—The patient had endured from six to eight epileptiform attacks. These consisted of an aura of "feeling hot all over," rolling of the eyes and dilatation of the pupils, which did not react to light. There was a jerking of the head, followed first by tonic and then a few clonic twitchings of the lower extremities. The deep reflexes were increased during the attack, and there was involuntary micturition.

The heart rate was irregular during this time. Immediately preceding an attack, the heart tones at the apex disappeared and the cardiac pulse was imperceptible. These conditions lasted for from fifteen to thirty seconds. Then the apex tones began again, one or two at a time at first and then more frequently at the close of the seizure, but with absolute irregularity. This state continued until the next attack, which was heralded by a gradual loss of the apex beat until it became entirely absent. The attacks occurred every five or ten minutes for forty minutes and then stopped. The rhythm gradually became regular, or nearly so, and the rate varied from 48 to 52 per minute. The pulse was of the bigemini type.

Examination of the heart some time after complete recovery from the attack revealed a moderate transverse enlargement. There were no murmurs, and the heart beat was regular and uniform, but feeble. The rate was 82 per minute.

The liver was slightly enlarged, and the entire abdomen was voluntarily rigid. Neurologic examination was entirely negative.

Urinalysis disclosed nothing, the Kahn reaction of the blood was negative, the Wassermann reaction of the spinal fluid was negative. The white blood count was 17,150, with 75 per cent polymorphonuclear leukocytes, 1 per cent eosinophils and 23 per cent lymphocytes.

An x-ray picture of the chest verified the transverse enlargement of the heart.

The electrocardiographic reading was as follows (Dr H J Isaacs): ventricular rate, 50, auricular rate, 135, complete heart block, right ventricular preponderance, marked notching of the Q-R-S complexes (fig 8c).

The diagnosis was acute to subacute myocarditis with superimposed heart block and a Stokes-Adams syndrome.

*Course*—While the patient was in the hospital he had numerous seizures, during which his heart rate would become low or absent, as described, but in the intervals his pulse was normal or elevated in rate, varying from 88 to 132 beats per minute. The pulse was irregular at times, but as a rule was regular and feeble. He continued to run an intermittent temperature (from 98 to 102 F [rectal]). Terminally, dyspnea, orthopnea and cyanosis set in. The patient died one week after the onset of acute symptoms and four months after his first complaints.

*Postmortem Examination* (Dr S R Rosenthal)—The body, weighing 135 pounds (61.2 Kg) and being 171 cm in length, was that of a strongly built boy, whose mucous membranes were pale. The skin of the neck and shoulders was discolored a deep purple red.

The heart weighed 500 Gm. The left ventricular wall was 15 mm in thickness, and the right ventricular wall was 4 mm. The myocardium was a glossy, red

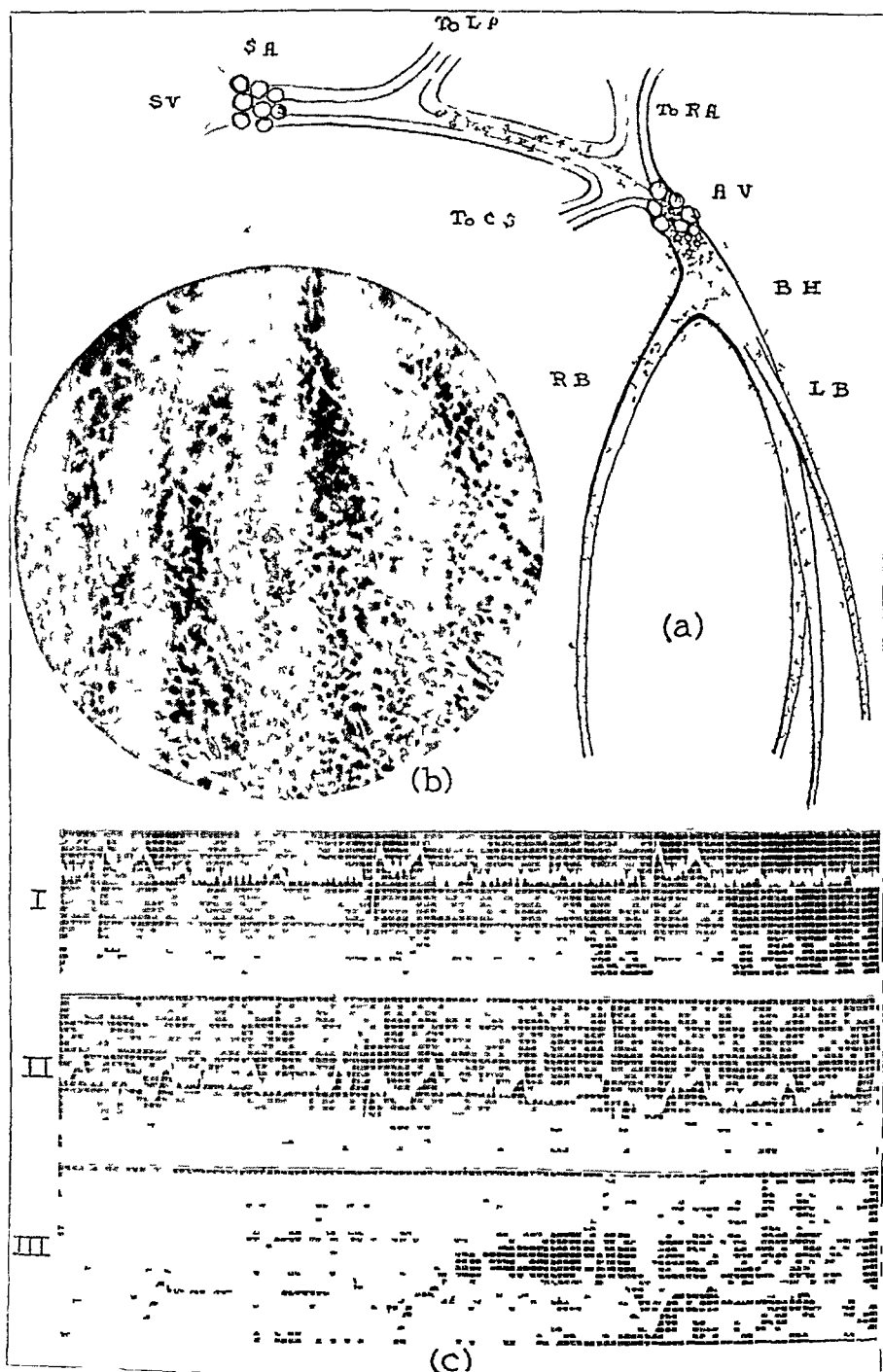


Fig 8—In *a* there is lymphocytic, histiocytic and granulocytic infiltration of the entire bundle of His and its branches *b* is a photomicrograph of the region of the bundle of His (reduced from  $\times 300$ ) *c* is an electrocardiographic tracing (three leads), showing complete heart block

brown mottled with tan. Its consistency was soft, especially near the apex, where the innermost portion of the myocardium of the left ventricle was pultaceous. A mural thrombus, measuring 4 by 2.5 by 2 cm, covered the softened area and was adherent to it. The endocardium of the remaining left ventricle was slightly thickened and pale gray, the trabeculae carneae were flattened. The circumference of the left ventricle was 110 mm, while the height was 90 mm. The right ventricle showed a moderate dilatation. The free margin of the posterior leaflet of the mitral valve was slightly thickened, and superimposed on this was a fine, granular deposit.

The coronary arteries were thin-walled and smooth. The aorta showed no gross changes.

TABLE 5—*Summary of Case 5*

	Diagnosis		
	Pathologic	Clinical	Electrocardiographic
Sino auricular node	No change	Subacute myocarditis with superimposed heart block and Stokes-Adams syndrome	Complete heart block, right ventricular preponderance, marked notching of Q R S complexes
Auricular fibrils	Moderate round cell infiltration		
Atrioventricular node	Interstitial infiltration of lymphocytes, monocytes and histiocytes		
Common bundle of His	Extravasation of blood with round cell and histiocytic infiltrations		
Left branch	Marked small round cell infiltrations, moderate number of histiocytes and polymorphonuclear leukocytes		
Right branch	Marked small round cell infiltrations, moderate number of histiocytes and polymorphonuclear leukocytes		
Arborizations	Marked infiltrations beneath endocardium of left and right ventricle of lymphocytes, histiocytes, and few granulocytes		
Comments	Fibroplastic deformity of the mitral valve with recent verrucous deposits		Myomalacia of left ventricle accounted for the right ventricular preponderance

The liver weighed 1,845 Gm, there was a fine fibrinous exudate on its capsule, and in the parenchyma were small areas of central red atrophy. The spleen weighed 270 Gm, and its capsule was covered by a fine fibrinous exudate. The pulp was deep red and soft, and the follicles were prominent.

The remaining organs were congested and occasionally showed small petechial hemorrhages.

*Microscopic Data*—Interventricular Cardiac Septum, Including the Posterior Wall of the Right Auricle (fig 8a and b). In the region of the atrioventricular node, a well isolated group of muscle fibers, which had ample sarcoplasm, presented an interstitial infiltration of small round cells, a few granulocytes and histiocytes. Many of the specialized muscle fibers were shrunken, had pyknotic nuclei and in places were entirely replaced by the cellular infiltrations. The remainder of the auricle showed a moderate perivascular round cell infiltration and a loss of cross-striations of the muscle fibers.

In the membranous portion of the interventricular septum, beneath the endocardium bordering the right ventricle, was a moderate extravasation of blood. A few mononuclear cells, scattered in small foci, prevailed throughout.

The most prominent changes were found in the muscular portion of the interventricular septum. It was extensively infiltrated, especially in its superior aspect, by small round cells and to a lesser extent by granulocytes, especially eosinophilic, and swollen adventitial cells. The exudate appeared most pronounced between the muscle bundles, but in many instances invaded the muscle cells and replaced them. Beneath the endocardium of both ventricles, the cellular extravasations arranged themselves in sheets beneath the endocardium. The latter was slightly thickened by edema and a proliferation of the lining cells.

The vessels were unusually dilated and toward the center of the septum were ruptured, and small extravasations of blood surrounded them.

By staining with the van Gieson method, an increase of fibrous tissue or scarring was noted in the muscular portion of the septum. In the region of the atrioventricular node, however, the muscle bundles were interspersed with fibrous strands that stained a deep red.

The elastic stain clearly demonstrated the marked dilatation of the vessels in the center of the septum, their ruptured internal elastic membranes and the escape of blood.

**The Superior Portion of the Right Auricle Near the Superior Vena Cava.** In the vicinity of the sino-auricular node was a wedge-shaped area beneath the endocardium, which was composed of large cells with ample vacuolization and deeply staining shrunken nuclei. Surrounding this node, for a short distance, the muscle bundles were infiltrated by small lymphocytes and fewer granulocytes. Although this exudate was most marked between the muscle fibers, there were also invasion and destruction of the muscle. On the whole, the invasion of the auricular musculature was negligible in comparison with the ventricular invasion.

**Anatomic Diagnosis.**—This was subacute myocarditis with invasion of the atrioventricular node, the common bundle of His and both branches, heart block (clinical), myomalacia of the apex of the left ventricle with mural thrombus formation, focal epicardial fibrosis over the anterior aspect of the apex of the left ventricle, slight fibroplastic deformity of the posterior cusp of the mitral valve with recent verrucous endocarditis of this leaflet.

#### COMMENT

Excluding extracardiac lesions, the pathologic changes that may affect the conducting apparatus and lead to heart block are as follows:

**Inflammation.**—Acute and Subacute. Notably in the course of diphtheria, endocarditis, pericarditis and nephritis, heart block may occur (Monckebeig,<sup>29</sup> Schmincke,<sup>30</sup> Aschoff,<sup>38</sup> Gerhardt,<sup>39</sup> Sternberg,<sup>40</sup>

<sup>38</sup> Aschoff, L. Referat über die Herzstörungen in ihren Beziehungen zu den spezifischen Muskelsystemen des Herzens, Verhandl d deutsch path Gesellsch **14** 3, 1910, Zur Frage der subendokardialen Blutungen, Virchows Arch f path Anat **213** 176, 1913.

<sup>39</sup> Gerhardt, D. Ueber Rückbildung des Adams-Stokes'schen Symptomenkomplexes, Deutsches Arch f klin Med **93** 485, 1908.

<sup>40</sup> Sternberg, C. Ueber Erkrankungen des Myokard, Wien klin Wchnschr **41** 1045, 1928, Beiträge zur Pathologie des Atrioventrikularbündels, Verhandl d deutsch path Gesellsch **14** 102, 1910.

Lasowsky,<sup>41</sup> Taussig,<sup>42</sup> Price and Mackenzie<sup>43</sup> and Rohmer<sup>44</sup>). The histologic picture is that of dense infiltrations of lymphocytes and polymorphonuclear leukocytes in the myocardium of both ventricles, especially the interventricular septum. The auricles are usually spared. The bundle of His and its branches are more frequently involved than the nodes. The sino-auricular node is rarely involved, while the atrio-ventricular node is relatively commonly affected (cases 4 and 5).

**Chronic.** Syphilis is the most common chronic inflammatory condition and may manifest itself as an interstitial myocarditis (Hill<sup>45</sup>) or a total gumma (Monckeberg,<sup>29</sup> van den Bovenkamp<sup>46</sup> T. Fahr<sup>46</sup> and Robinson<sup>47</sup>). Aneurysms interrupting the bundle of the atrioventricular node have been described by Roth<sup>21</sup> (case 1). A tuberculosis lesion involving the sino-auricular node has been described by Ceelen<sup>48</sup>.

**Vascular.**—Atherosclerosis. Sclerosis of the coronary artery may lead to fibrotic, calcific and fatty changes of the nodes, the bundle of His and the myocardium (Monckeberg,<sup>29</sup> Engel,<sup>49</sup> Fleming and Kennedy,<sup>50</sup> Geraudel, Brodin and Lereboullet<sup>51</sup> and Barnes and Yater<sup>52</sup>). However, complete intersection of the bundle must exist before clinical signs of block will be evident (case 2).

41 Lasowsky, J. M. Normale und pathologische Histologie der Herzzanglien der Menschen, *Virchows Arch f path Anat* **279** 464, 1931.

42 Taussig, H. B. A Case of Bundle Branch Block Confirmed by Pathological Study, *Bull Johns Hopkins Hosp* **45** 40, 1929.

43 Price, F. W., and Mackenzie, I. Auricular Fibrillation and Heart Block in Diphtheria, *Heart* **3** 233, 1912.

44 Rohmer, P. Neuere Untersuchungen über den Diphtherieherztod, *Jahrb f Kinderh* **76** 361, 1912.

45 van den Bovenkamp, G. J. A Case of Total Heart-Block from a Gumma, *Nederl tijdschr v geneesk* **68** 1502, 1924.

46 Fahr, T. Anatomische Beiträge zur Frage der Herzinsuffizienz, *Verhandl d deutsch path Gesellsch* **14** 105, 1910.

47 Robinson, G. C. Gumma of the Heart from a Case Presenting the Symptoms of Adams-Stokes' Disease, *Bull Ayer Clin Lab Pennsylvania Hosp* **4** 1, 1907.

48 Ceelen, W. Das Reizleitungssystem des Herzens, *Berl klin Wchnschr* **56** 509, 1919.

49 Engel, Irmgard. Beiträge zur normalen und pathologischen Histologie des Atrioventrikulärbündels, *Beitr z path Anat u z allg Path* **48** 499, 1910.

50 Fleming, G. B., and Kennedy, A. M. A Case of Complete Heart-Block in Diphtheria, with an Account of the Post-Mortem Findings, *Heart* **2** 77, 1910.

51 Geraudel, E., Brodin, P. L., and Lereboullet, J. Étude d'un cas de syndrome d'Adams-Stokes mortel. Nécrose transverse du ventriculo-necteur par endarterite sténosante de son artère, *Arch d mal du cœur* **22** 1, 1929.

52 Barnes, A. R., and Yater, W. M. Paroxysmal Tachycardia and Alternating Incomplete Right and Left Bundle-Branch Block with Fibrosis of the Myocardium, *M Clin North America* **12** 1603, 1929.

**Thrombosis** Thrombosis or embolism of the coronary arteries with infarction of the interventricular septum may lead to a complete heart block (Brinck, Miszke and Schone<sup>21</sup> and case 2)

**Endarteritis** Endarteritis of the vessels supplying the bundle of His may lead to a fibrosis or necrosis of the same (Géraudel and Gautier<sup>53</sup>)

**Hypertension** In the literature, no mention is made of the mechanism by which heart block results in a hypertensive heart. Pre-stasis and stasis of the precapillaries and capillaries as a result of an increased tonus of the smallest arteries and arterioles lead to degenerative changes of the supplied parenchyma. Because the bundle of His is so richly supplied with blood vessels, the former becomes especially prone to vascular alterations (case 3)

**Toxic—Drugs** Overdoses of digitalis have been repeatedly reported as producing heart block (Aschoff,<sup>38</sup> Monckeberg<sup>29</sup> and Cohn and Lewis<sup>16</sup>) This is explained by Aschoff on the basis of hemorrhages that occur subendocardially and within the bundle of His as a result of violent contractions of a damaged myocardium

**Bacterial Toxins** In the early stages of diphtheria (Monckeberg,<sup>29</sup> Butler and Levine<sup>54</sup> and Aschoff<sup>38</sup>), in tetanus (Ribbert<sup>55</sup>) and in intestinal toxemias (Taylor<sup>56</sup>), extensive hemorrhage may be found in the interventricular septum. This is a result of the severe degenerative changes in the myocardium, which ruptures as a result of the contractions (Berblinger,<sup>57</sup> Amenomiya,<sup>58</sup> Rohmer,<sup>44</sup> Magnus-Alsleben<sup>59</sup> and Fleming and Kennedy<sup>50</sup>) Direct vascular damage may also be responsible for extravasations of the blood or for myolysis (Monckeberg<sup>29</sup>)

**Neoplastic**—Primary sarcomas of the heart leading to block are exceedingly rare. A lymphangio-endothelioma of the atrioventricular

53 Geraudel, E, and Gautier, C. Syndrome d'Adams-Stokes par necrose transverse du ventriculo-necteur consecutive a une endarterite oblitterante de son artere, *Ann d'anat path* **8** 339, 1931

54 Butler, S, and Levine, S. A. Diphtheria as Cause of Late Heart-Block, *Am Heart J* **5** 592, 1930

55 Ribbert, H. Ueber die subendokardialen Blutungen im Bereiche des Atrio-ventrikularbundsels, *Deutsche med Wchnschr* **41** 211, 1915

56 Taylor, F. I. A Case of Transient Heart Block Due to Intestinal Toxemia, *J A M A* **50** 1246 (April 18) 1908

57 Berblinger, W. Ueber die subendokardialen Blutungen, die Beziehungen zwischen Blutung und Degeneration der Herzmuskelfasern, *Centralbl f allg Path u path Anat* **28** 1 1917

58 Amenomiya, R. Ueber das Atrioventrikularbundel des Herzens bei Diphtherie, *Virchows Arch f path Anat* **202** 107, 1910

59 Magnus-Alsleben, E. Zur Kenntnis der vorubergehenden Ueberleitungsstörungen des Herzens, *Ztschr f klin Med* **69** 82, 1909

node was described by Lloyd,<sup>60</sup> as well as by Armstrong and Monckeberg.<sup>61</sup> A fibroxanthosarcoma was described by Dietrich<sup>62</sup> and a rhabdomyoma by Bundschuh<sup>63</sup> and Monckeberg.<sup>29</sup> Metastatic carcinomas have been described by Monckeberg.

*Congenital*—Several cases have been reported of complete heart block as a result of congenital defects of the interventricular septum, especially the membranous portion, which is the last to fuse (Brandenburg<sup>64</sup>).

*Traumatic*—An injury in the region of the precordium, producing a complete heart block which lasted over several years, was reported by Coffen.<sup>65</sup>

*Senile*—In elderly people, degenerative changes of the conducting system are common, but block is rare (Bonniger and Monckeberg<sup>66</sup>). In heart diseases of all types, Sternberg<sup>40</sup> found anatomic lesions in the bundle in 70 per cent. Brown atrophy with fibrosis and calcific changes producing block has been described by Lasowsky.<sup>41</sup>

*Functional*—This type of block cannot be accepted as a true entity, for in such cases that have been reported either no postmortem findings were given or thorough histologic studies were wanting (Hume<sup>67</sup> and Mollard, Dumas and Rebattu<sup>68</sup>). Gerhardt's<sup>39</sup> observation is illuminating in this regard. His patient had several attacks of heart block in the course of rheumatic fever. The attacks lasted from two to three weeks at a time and were associated with an Adams-Stokes syndrome. The

60 Lloyd, P. C. Heart Block Due to Primary Lymphangio-Endothelioma of the Atrio-Ventricular Node, Bull. Johns Hopkins Hosp. **44** 149, 1929.

61 Armstrong, H., and Monckeberg, J. G. Herzblock, bedingt durch primären Herztumor bei einem 5-jährigen Kinde, Deutsches Arch. f. klin. Med. **102** 144, 1911.

62 Dietrich, A. Ueber ein Fibro-xanthosarcoma mit eigenartiger Ausbreitung und über eine Vena cava superior sinistra bei dem gleichen Fall, Virchows Arch. f. path. Anat. **212** 119, 1912.

63 Bundschuh, E. Ein weiterer Fall von tuberöser Sklerose des Gehirns mit Tumoren der Dura mater, des Herzens und der Nieren, Beitr. z. path. Anat. u. z. allg. Path. **54** 278, 1912.

64 Brandenburg, K. Dauernder vollständiger Vorkammer-Kammerblock bei einem 4-jährigen Knaben—angeborener Herzfehler, subaortaler Septumdefekt, Med. Klin. **25** 1464, 1929.

65 Coffen, T. H. Complete Heart-Block of Seven Years' Duration in a Child Resulting from an Injury, Am. Heart J. **5** 667, 1930.

66 Bonninger, M., and Monckeberg, J. G. Untersuchungen über das Atrio-ventrikulärbandel des menschlichen Herzens, Deutsche med. Wchnschr. **34** 2293, 1908.

67 Hume, W. E. A Case of Heart-Block in Which There Was No Pathological Lesion of the Connecting Muscular System, Heart **5** 149, 1914.

68 Mollard, J., Dumas, A., and Rebattu, J. Syndrome de Stokes-Adams, sans lésion du faisceau de His, Arch. d. mal. du cœur **4** 298, 1911.



patient recovered clinically, but died a few months later of typhoid fever. Histologic studies of the heart disclosed red cell infiltrations and sclerosis of the vessels within the bundle.

#### SUMMARY AND CONCLUSIONS

Although single pathologic cases cannot unconditionally confirm or refute experimental results, their importance is singular when they reduplicate experimental conditions. The aneurysm of the sinus of Valsalva involving only the left branch of the bundle of His, and its prediction by the dextrocardiogram strongly support the original work of Epping and Rothberger<sup>9</sup> and question the interpretation of Wilson, Macleod and Barker.<sup>13</sup> Strengthening this doubt are the correspondence anatomically of left over right ventricular hypertrophy with its verification by the electrocardiogram.

Arborization block per se cannot be considered as a distinct entity and when present is associated with an interruption of one or both of the main branches of the bundle. Coronary sclerosis with infarction of the interventricular septum or chronic myocarditis with marked scarring may produce the aforementioned lesion. Acute inflammations will not produce an arborization block, because the destruction of the arborizations is probably not complete.

Acute or subacute myocarditis may lead to heart block by invasion of the atrioventricular node, the bundle of His or its branches. Endocarditic lesions were found in the two cases of myocarditis reported, one being microscopic in size and the other focal and small. Because of the cases reported in the literature as myocarditis of unknown origin, in which few or no microscopic studies were made, it is suggested that the endocarditic lesions may have been microscopic and overlooked.

In a case of essential hypertension with heart block, the mechanism by which the degenerative changes took place in the bundle of His is explained by an increased tonicity of the small arteries and the arterioles and prestasis and stasis in the precapillaries and capillaries.

The various processes producing heart block, as deduced from the five cases reported and the literature, are presented

# STENOSIS OF THE SUPERIOR VENA CAVA DUE TO MEDIASTINAL TUBERCULOSIS

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Obstruction of the superior vena cava is the cause of the outstanding symptoms in many cases of mediastinal pathologic conditions. However, isolated stenosis of this vessel is distinctly rare.

Interference with the return flow of blood to the heart through the superior vena cava may arise from a wide variety of conditions in the mediastinum or in the vessel itself.

Of the diseases, aneurysm,<sup>1</sup> almost universally of the aorta, is the most common. This lesion may compress and thereby result in slow partial mechanical obstruction of the superior vena cava and give rise to a train of symptoms due to this compression and compression of other mediastinal structures, such as the recurrent laryngeal nerves, trachea and esophagus. On the other hand, an aneurysm of the aorta may perforate into the vein, producing sudden functional stenosis of the vena cava as a result of the tremendous head pressure opposing the returning venous blood.

Mediastinal tumors are a common cause of superior caval obstruction, and present symptoms of this condition plus symptoms of compression of the other mediastinal structures. In this group are primary mediastinal tumors arising from the thymus,<sup>2</sup> substernal nodular goiter, carcinoma of a substernal thyroid and fibroma<sup>3</sup> and sarcoma of the mediastinum.

Metastasis or extension of a tumor into the mediastinum may give rise to caval obstruction. By far the most common tumors in this group are the bronchogenic carcinomas,<sup>4</sup> which are increasing in frequency.

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1 Packard, M, and Wechsler, H F. *Am Heart J* 6 281, 1930.

2 Brannan, D. Carcinoma of the Thymus and Occlusion of the Superior Vena Cava, *Arch Path & Lab Med* 1 569 (April) 1926. Foot, N C. *Am J Path* 2 33, 1926.

3 Pastau. Virchows *Arch f path Anat* 34 236, 1865.

4 Brown A L. Complete Occlusion of the Superior Vena Cava by Primary Carcinoma of the Lung, *Arch Surg* 21 959 (Dec) 1930. Dana, H W, and McIntosh, R. *Am J M Sc* 163 411, 1922.

Hodgkin's disease<sup>5</sup> and the leukemia<sup>6</sup> cause symptoms of venous obstruction in this region

Mediastinitis is liable to give rise to isolated or to a caval obstruction by pressure, constriction of the vein by scar tissue, secondary phlebitis and even endophlebitis. Here tuberculosis is the most common, either as localized tuberculosis of the mediastinal lymph glands or as extension from a tuberculous lesion in the lung. Syphilis of the mediastinum,<sup>6</sup> echinococcus disease in the mediastinum, extension of rheumatic pericarditis and nonspecific mediastinitis with secondary arteriovenous aneurysm<sup>7</sup> have been described as causes

Thrombosis of the primary superior vena cava, following influenza<sup>8</sup> due to secondary phlebitis<sup>9</sup> or by extension of thrombus from tributary veins has been observed

The symptoms arising from superior vena caval obstruction are the result of venous stasis in the parts drained and attempts to compensate for it. The superior vena cava drains the head and neck, the upper extremities and the thoracic wall to the level of from the fourth to the sixth ribs. Occlusion of the vein results in variable degrees of edema and cyanosis of these parts. The attempt to compensate results in dilatation of the tributary vessels with reversal of flow in those leading ultimately to the inferior vena cava.

It is noteworthy that the edema is most prominent in the head and neck and least prominent in the arms. This is probably the result of the auxiliary effect of the voluntary muscles in propelling the blood through the veins. Further, the edema and all other symptoms are accentuated by changes in posture that lower the upper half of the body in relation to the lower half, thus preventing gravity from aiding the return flow of blood to the heart. The subjective symptoms of superior caval stenosis are due chiefly to the marked passive congestion of the brain.

The clinical picture is a varying blend of venous obstruction and distention of the collateral circulation, depending on the rapidity of development and the degree of stenosis obtaining, and is more or less modified and often completely obscured by the concomitant effects of pressure on other mediastinal structures.

The picture seen in pure superior caval stenosis may be acute or chronic, the latter varying in degree.

5 Osler, W. Bull. Johns Hopkins Hosp. **14** 169, 1903

6 Fraenkel. Deutsche med. Wchnschr. **17** 1378, 1891

7 Chiovenda, M. Arch. ital. di anat. e istol. pat. **1** 409, 1930

8 Strauss, A. Schweiz. med. Wchnschr. **59** 1410, 1929

9 Perla, D., and Seligman, B. Diffuse, Obliterating Endarteritis of Unknown Etiology. An Instance with Obliteration of the Inferior Vena Cava, Arch. Path. **7** 55 (Jan.) 1929

Thus the fulminating head cyanosis resulting from the sudden over-aneurysm perforates entered by the venous blood when an he superior vena cava gives rise to a dramatic, suddenly developing cyanosis of the upper half of the body, sharply demarcated at the level of the same area. Engorgement is especially prominent in the large veins, such as the jugular veins, but is also to be seen in the veins of the conjunctiva and eyegrounds. Edema of the conjunctiva with suffusion and papilledema are present. Subjectively dyspnea and orthopnea develop with almost explosive violence. Death usually intervenes early as the result of cerebral edema and congestion or of the primary pathologic process.

Gradually developing superior caval obstruction may result from any of the causes mentioned, and gives rise to a more or less insidiously developing train of symptoms which is toned down by the development of the collateral circulation. Thus the cyanosis is moderate, most pronounced inferiorly limited to the head and neck or seen only in the mucous membranes of the mouth and conjunctiva. The edema is variable and limited to the head and neck, associated with suffusion, it is usually present in the conjunctiva. Engorgement of the cervical veins is pronounced, and, with the associated edema of the neck, gives rise to an increasing collar size. The superficial collateral veins are prominent, especially about the costal margins and to a lesser extent over the upper part of the abdomen and the upper section of the thorax. Polycythemia has been reported as occurring in the upper half of the body and later becoming generalized<sup>10</sup>. A similar phenomenon has been reported in the lower half of the body in cases of obstruction in the inferior vena cava<sup>11</sup>.

Subjectively the symptoms are dyspnea, orthopnea, dizziness, fulness in the head and constant sleepiness.

Obstruction to the flow of blood through the superior vena cava is not fatal per se, except when the onset is acute. This is attested to by one case of thirty years' duration that has been reported<sup>12</sup>. Death is the result of the underlying or associated pathologic conditions. In the rare long-standing cases all symptoms are slight, and the collateral circulation is abundant. However, the reserve is minimal, so that exertion will induce the symptoms even to an alarming degree.

#### REPORT OF A CASE

A white man, aged 42, an ex-prizefighter, was first seen on Feb 5, 1931. He complained of dizziness, dyspnea, orthopnea, swelling of the face and neck and sleepiness. He had been well until the summer of 1930, when he noted dyspnea

10 Reckzeh *Ztschr f klin Med* **57** 215, 1905. Abramson *California State M J* **10** 14, 1912.

11 Tumen, H J *Am J Obst & Gynec* **20** 417, 1930.

12 Clavierie, G E *These de Paris*, no 4, 1858.

on exertion, dizziness, orthopnea and drowsiness. At about the same time his face and neck began to swell and his collar size to increase. These symptoms were slowly progressive and were accentuated on exertion, at night, and during the following months the swelling of the face and neck increased in degree, depending on the physical activity of the patient. In about 1930, choking spells and extreme orthopnea disturbed him at night, and the eyes became almost constant. A slight, rather insignificant edema appeared and he lost about 6 pounds (2.7 Kg.).

The patient was well nourished, exceptionally well developed, short and stocky. The face and neck were definitely edematous, and the lips were slightly cyanotic, and the conjunctivae were injected and enlarged. The jugular veins were distended, and prominent varices encircled the neck margin.

Slight widening of the upper mediastinal dulness was noted on percussion. The blood pressure was 128 systolic and 78 diastolic in both arms. Laboratory examination revealed 10.5 Gm of hemoglobin (Newcomer), 50,000 red blood cells and 5,350 white blood cells, with 40 per cent lymphocytes. The Wasser-



Fig 1—Photograph of the patient one and one-half years after the onset of stenosis of the superior vena cava. Edema is noted most prominently about the eyelids and neck but is nowhere very marked.

Mann and Kahn tests were negative, the chemical examination of the blood gave normal results, and the urine was normal.

Roentgenograms and fluoroscopic examination revealed a slightly widened upper mediastinal shadow, which was interpreted as a tumor, no evidence of aneurysm was found.

Deep roentgenotherapy caused no change in the clinical findings during the following months. However, the hemoglobin was increased to 16.5 Gm (Newcomer), and the red blood cell count to 5,480,000. The patient was observed until November, 1931, when he began to complain of increase in dyspnea, although objectively little change had occurred. The cause of the obstruction was thought to be a benign tumor, and in view of the hopeless outlook mediastinal exploration was undertaken by Dr. Lindon Seed.

Tremendously dilated superficial veins were encountered when the skin was incised. The right internal mammary vein was found to be about 8 mm in diameter, when it was opened a stream of blood was thrown 20 cm from the upper end. The mediastinum was widely exposed, but no tumor could be demon-

strated superior vena cava was distended, blue and thick-walled. The wound was closed and the patient returned to bed apparently in good condition. On the following day the edema of the head and neck was increased, the arms were swollen and cyanosis and dyspnea were pronounced. Respirations became rapid and shallow and the edema of the face, neck, and chest more pronounced, and the patient died on the fourth day after operation.

At autopsy the superficial internal mammary, azygos and superior epigastric veins were markedly dilated. A cartilaginous, rather poorly defined mediastinal mass was found adherent to the lung and encircling the superior vena

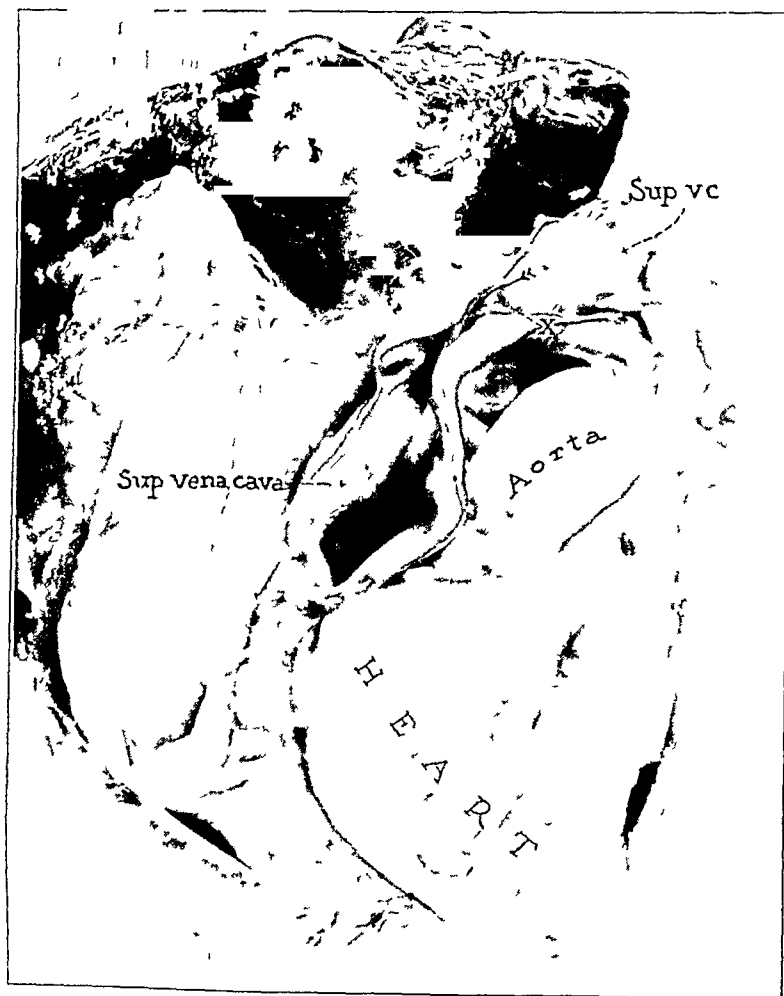


Fig 2—Stenosis of the superior vena cava. X indicates a dense valvelike flap completing the stenosis. The arrow indicates the passage, 2 mm in diameter, that remains.

cava about 4 cm above the right auricle. When the vessel was opened, its lumen in this region was demonstrated to be 2 mm in diameter, the wall was thickened to 7 mm by dense cartilaginous connective tissue, and the center of the encircling mass was made up of cheesy, necrotic material of the shape and appearance of a broken-down lymph gland. Above the point of stenosis the vessel was dilated moderately. The remaining organs were free from demonstrable pathologic conditions.

Microscopic sections through the area of sterile caseation necrosis. About this was a dense, hypercellular connective tissue stroma which was the seat of a diffuse and focal infiltration of lymphoid and epithelioid cells, fibroblasts, a few Langhans giant cells, and occasional macrophages. No tubercle bacilli could be identified in sections stained by the Ziehl-Neelsen method. However, macrophages containing a few acid-fast granules of varying sizes were noted.

In view of the caseation necrosis and the location and the presence of the microscopic features described, in the absence of syphilitic features, either gross or microscopic, a diagnosis of chronic fibrocaceous tuberculosis of a mediastinal lymph gland was made. Death had resulted from the destruction of a considerable part of the collateral circulation in the absence of an appreciable circulatory reserve. The stenosis of the superior vena cava making this collateral circulation necessary had resulted from the extension of caseous lymph gland tuberculosis of the mediastinum with a marked desmoplastic reaction to involve the superior vena cava.

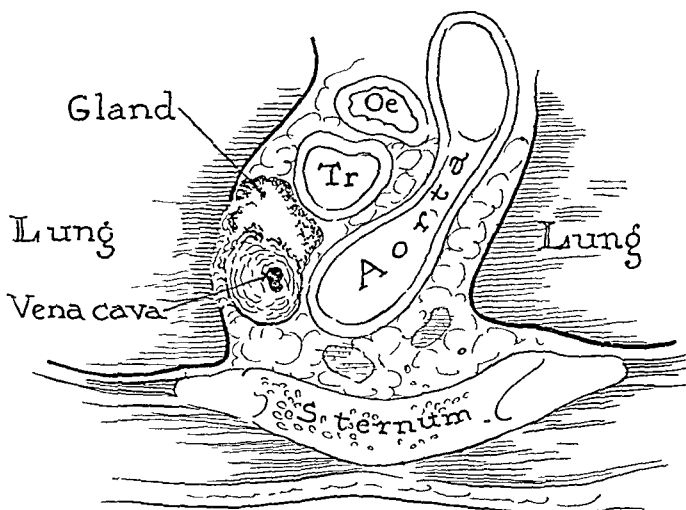


Fig. 3—Diagrammatic sketch indicating the level of the stenosis and the relation of the caseous lymph glands to the vena cava and the lung.

#### COMMENT

This case illustrates the clinical picture of a chronic, rather slowly developing stenosis of the superior vena cava with terminal, rather acute obstruction. The complaints of dyspnea and orthopnea were dependent on the cerebral passive congestion with the concomitant increase in carbon dioxide in the cerebral circulation, resulting in respiratory stimulation. The drowsiness and probably the dizziness were caused by impaired cerebral circulation, with the resultant lowering of the metabolic possibilities of the vital centers. The limitation of the edema to the head and neck until the collateral circulation was suddenly reduced is explainable by the aid given the venous return by the skeletal muscles, while the effect of gravity in this regard explains the aggravation of the symptoms on stooping. The lack of reserve potentialities

in the upper half of the body explains the aggravation of symptoms on exertion and the acute exacerbation of symptoms and death. The removal of part of the collateral circulation (right internal primary vein)

Another phase of this case must be emphasized, namely, the etiology of the caval stenosis. Mediastinal tuberculosis in adults without demonstrable lesions or with only an old healed primary lesion in the pulmonary parenchyma is explainable on the basis of reactivation of the tracheobronchial lymph gland infection of the primary complex. It accounts for some of the pulmonary tuberculosis of adults, but offers almost insurmountable diagnostic difficulties when the pulmonary involvement is slight or absent.

The writer has encountered mediastinal tuberculosis giving rise to a cold abscess of the mediastinum with toxic nephrosis and finally extension into the pericardial sac to give rise to tuberculous pericarditis, or breaking into the general circulation and giving rise to miliary tuberculosis of the spleen, liver and kidneys with terminal pulmonary miliary tuberculosis. Instances of similar involvement of the esophagus<sup>13</sup> with traction diverticula, hemorrhage with sudden death<sup>14</sup> or tracheoesophageal fistula resulting are reported in the literature.

The roentgen findings in mediastinal tuberculosis are negative or at times misleading unless the glandular involvement is marginal and discrete or the seat of calcium infiltrations<sup>15</sup>. Therefore, mediastinal tuberculosis must be thought of as a possibility in obscure cases of mediastinal pathologic conditions and as the source of miliary tuberculosis or its clinical picture.

#### SUMMARY

1 The symptoms of vena caval obstruction are due to venous congestion and edema, are modified according to the degree of collateral circulation obtaining and are confused or obscured by other symptoms arising directly or indirectly from the underlying pathologic condition.

2 A case of tuberculosis of the tracheobronchial lymph glands causing superior caval stenosis is described.

3 The importance of mediastinal tuberculosis as the cause of a variety of clinical pictures is indicated.

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13 Smellie, J. M. *Brit J Child Dis* **20** 110, 1925

14 Callis, H. A. *Am J Clin Path* **1** 51, 1931

15 McPhedan, F. M. *Am J M Sc* **173** 245, 1927 Kornblum, K., and Cooper, D. A. *Am J Roentgenol* **23** 276, 1930



# COMBINED ACTIONS OF QUINIDINE AND DIGITALIS ON THE HEART

AN EXPERIMENTAL STUDY

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## INTRODUCTION

Pharmacologic studies of the combined actions of digitalis and quinidine derive interest largely from the fact that while the two drugs possess some actions in common, they produce, with reference to certain other phenomena, diametrically opposite effects. Such studies have a direct practical bearing as well, because the two drugs are used together widely, especially in the treatment of patients with auricular fibrillation. Many of the clinical observations on quinidine have been made in digitalized patients. In these the fact that the heart may have been fully under the influence of digitalis frequently receives only casual mention or is even overlooked, and the appearance of toxic effects is ascribed to the action of quinidine alone, although some of these effects are never seen in normal animals after comparable doses of quinidine.

Experimental studies of the combined action of the two drugs in animals have not been very comprehensive, and investigations of their combined use in man have not gone materially beyond their actions on the fibrillating auricle. In view of the complexity of the actions of both quinidine and digitalis when used alone, and the variations in the effects in different species and with different doses, it becomes necessary to exercise extreme caution in drawing clinical inferences from the limited experimental results, these having been obtained in most instances under highly artificial conditions (morphine, ether or chlorbutanol anesthesia, thorax open, blood pressure low, massive doses of the drug).

The present investigation was undertaken to study one phase of the problem electrocardiographically in the normal unanesthetized dog. As quinidine is known to abolish various ectopic rhythms—auricular flutter

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and fibrillation, ventricular premature contractions<sup>1</sup> and ventricular tachycardia<sup>2</sup>—attention was directed chiefly to the effect of quinidine in the presence of an ectopic rhythm that is induced by digitalis most consistently, namely, ventricular tachycardia.

Rather striking results have been obtained. They show that quinidine and digitalis together produce effects that are almost never seen with either of the drugs alone under the same experimental conditions, that in the heart poisoned by digitalis, quinidine under some conditions may exert an apparently favorable influence and temporarily abolish the toxic rhythm induced by digitalis, but with change in the conditions, it may provoke serious reactions that may even prove fatal in doses that are never fatal in the normal undigitalized animal and that are comparable to those well within the range of therapeutic doses for man.

The details of these experiments and their interpretation form the subject of the present report.

#### EXPERIMENTAL WORK

Sixteen experiments were carried out on eleven dogs. Three of the normal animals had been used from two to six days previously for the study of the action of quinidine alone, and serve to compare the effects of quinidine before and after digitalis in the same animal. The experimental procedure was essentially similar to that in the previous study.<sup>3</sup> Only such animals were selected as would remain perfectly quiet without restraint while the electrocardiographic tracings were taken and while the injections were being made. Three animals (five experiments) were vagotomized, the vagi being severed in the neck during light ether anesthesia. In these at least two hours elapsed before any injections were made, in order to allow for recovery from the anesthesia.

The cardiac changes were studied by means of electrocardiographic tracings, lead II only being used. Control records were made before any drug was given. After the animal was digitalized, tracings were taken at intervals to determine the changes in rhythm and the permanence of the desired ectopic rhythm. When the quinidine was given, a fairly uniform procedure was followed, the tracing being taken continuously before, during and for varying periods after the injection. In some the continuous tracings represented periods as long as four minutes. Between injections shorter tracings were taken at intervals varying from ten to fifteen minutes, but the galvanometer string was

1 Otto, H. L., and Gold, H. Persistent Premature Contractions, *Arch. Int. Med.* **38** 186 (Aug.) 1926.

2 Levine, S. A., and Fulton, N. M. The Effect of Quinidine Sulphate on Ventricular Tachycardia, *J. A. M. A.* **92** 1162 (April 16) 1929.

3 Gold, H., and Modell, W. The Action of Quinidine on the Heart in the Normal Unanesthetized Dog. *J. Pharmacol. & Exper. Therap.*, to be published.

observed almost continuously, and if any changes took place additional tracings were taken. In this way it was possible to record the immediate as well as the later effect of quinidine and also to determine the duration of the effects. From nine to thirty electrocardiograms of various length were taken in the course of each experiment.

A tincture of digitalis (the alcohol evaporated off with moderate heat) was injected intravenously in total doses varying from 0.5 to 1.5 cat units per kilogram<sup>4</sup> given in fractional doses. It was necessary to give such large doses of digitalis because with the lesser doses of poisoning the ventricular tachycardia tends to be paroxysmal, disappearing with changes in respiration or slight movement.<sup>5</sup> Quinidine sulphate was used in a 1 per cent solution made up in physiologic solution of sodium chloride. It was also injected intravenously in single doses varying from 1 to 16 mg per kilogram,<sup>4</sup> and in total doses ranging from 2 to 47 mg.

In one animal an attempt was made to study the effects of quinidine by intramuscular injection. The results were duplicated in some of the experiments after the intravenous injections, a ventricular tachycardia disappearing about fifteen minutes after a dose of 10 mg. These injections, however, were painful and since the delay in the onset of changes introduced uncertainties into the interpretation of the results, intramuscular injections were not continued in other experiments.

Abridged protocols of the experiments are given in table 1. Only significant tracings are included. Time is represented in minutes and seconds from the beginning of the experiment. The period of the injection was recorded on the tracings, and the time stated in the table signifies the completion of the injection which, depending on the size of the dose, varied from about five to twenty-five seconds. Ventricular rates were determined from a count in from six to twelve second strips. In the presence of ventricular tachycardia, the P waves were often obscured in the Q-R-S groups, which made the determination of the auricular rate often impossible, hence only in those cases in which a few successive P waves appeared in the records was the sinus rate ascertained. Figures for the P-R intervals, whenever possible, represent the average of ten readings.

## RESULTS

The injection of quinidine in dogs in which digitalis has produced a ventricular tachycardia results in a variety of changes depending on individual differences in the animal, the intensity of the digitalis poisoning and the doses of quinidine. It will not be feasible to discuss all the

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<sup>4</sup> All doses were given in milligrams per kilogram, but for the sake of brevity "per kilogram" will not be repeated throughout the paper.

<sup>5</sup> Gold, H., Liebersohn, A., and Gelfand, B. Mechanism of Production of Subauricular Beats by Digitalis Bodies, *Arch Int Med* 48:262 (Aug) 1931.

TABLE 1—*Abridged Protocols of the Experiments*

Time	Tracing	Rate		P R Inter- val	Comment
		Auricle	Ventricle		
<b>Experiment M</b>					
77'	8a		170		Digitals at 46 and 79 minutes
93' 9"					Ventricular tachycardia
96' 10"	8c		185		Quinidine 2 mg
98' 30"	8d	136	160		Ventricular tachycardia
102'	9		180		Ventricular tachycardia
224'					Vomited
230'	13a		230		Ventricular tachycardia
234'					Quinidine 1 mg
234'	13c		170		Ventricular tachycardia
<b>Experiment N</b>					
236' 15"	10r		160		Digitals at 14, 226 and 232 minutes
236' 30"					Ventricular tachycardia
236' 40"	10'	A*	125-A		Quinidine 5 mg
237' 30"	10c	150	150	0 14	Ventricular tachycardia, followed by asystole for 0.8 second
262' 30"	14a	190	190		Sinus rhythm, lasting about 11 minutes with rate up to 180
263'					Ventricular tachycardia
263' 30"	14b	190	160		Quinidine 5 mg
273'	15a	190	220		Ventricular tachycardia
273' 10"					Ventricular tachycardia
273' 20"	15b	160 A	125 A		Quinidine 10 mg
					Ventricular tachycardia, followed by stand still of ventricle for 24 seconds and of auricle for 10 seconds, convulsion
274' 30"	15d		180		Ventricular tachycardia
299'	16a		200		Ventricular tachycardia
299' 10"					Quinidine 10 mg
299' 30"	16b		210		Ventricular tachycardia, multiple foci
312'	17		200		Ventricular tachycardia, multiple foci, found dead following morning
<b>Experiment P 1 † (5/27/31)</b>					
86'	8a		260		Digitals at 15, 47 and 18 minutes
86' 30"					Ventricular tachycardia
89'	9a		230		Quinidine 2 mg
89' 30"					Ventricular tachycardia
90'	9b	160	200		Quinidine 4 mg
92' 30"					Ventricular tachycardia
94'	11	200	200	0 10	Quinidine 4 mg
101' 30"	13	150	150	0 10	Sinus rhythm
110'	14a	200	220		Ventricular ectopic beats appear
110' 15"					Ventricular tachycardia
111'	14c	250	250	0 10	Atropine sulphate 1 mg
117'	15	230	230		Sinus rhythm
					Ventricular tachycardia
<b>Experiment P 2 (5/28/31)</b>					
18'	6a		240		Digitals at 10 minutes, marked A V block
79'					Ventricular tachycardia
80'	6b		250		Quinidine 2 mg
83' 15"					Ventricular tachycardia
84'	7b		250		Quinidine 2 mg
92' 45"					Ventricular tachycardia
114' 30"	8a		210		Quinidine 4 mg
115' 45"					Ventricular tachycardia
116'	8b	250	A		Quinidine 4 mg
118'	8d	250	140		Asystole for 5 seconds
151'	9	250	140		A V dissociation with nodal beats
					A V dissociation with frequent ventricular and nodal beats
<b>Experiment T 2</b>					
52'	5a		240		Digitals at 3, 25 and 40 minutes
52' 10"					Ventricular tachycardia
63'	6a		240		Quinidine 5 mg
					Ventricular tachycardia, Q R S of varying forms
63' 15"					Quinidine 10 mg
65'	6b	160	130		Idioventricular rhythm, Q-R S of varying forms, this rhythm lasted 2½ minutes
71'	7a		220		Ventricular tachycardia
71' 10"					Quinidine 5 mg
72'	7b	190	115		Idioventricular rhythm
80' 55"					Quinidine 5 mg
81'	9b	210	75		Idioventricular rhythm
82'	9c		150		Idioventricular rhythm
97'	11	210	80		Ventricular tachycardia
101'	12	210	60		Idioventricular rhythm
113'	13	250	195		Idioventricular rhythm
					Ventricular tachycardia established during retching

\* 1 systole

† The experiments are designated so as to indicate when an animal was used on more than one day. For example, experiments P 1 and P 2 indicate that animal P was used for two separate experiments.

TABLE 1—*Abridged Protocols of the Experiments—Continued*

Experiment	Time	Tracing	Rate		P R Inter val	Comment
			Auricle	Ventricle		
Experiment T 2—Continued						
147'	15		210	75		Idioventricular rhythm
257'	24a			200		Digitalis at 220 and 244 minutes
257' 5"						Ventricular tachycardia
257'15"	24b	A	70			Quinidine 5 mg
	24c		150			Idioventricular rhythm
	24d	200	A			Ventricular tachycardia
	24e	214	90			Asystole lasted 5 seconds
361'15"	24f		170			Idioventricular rhythm
347'	2g		75			Ventricular tachycardia
						, round dead following morning
Experiment J 1 (5/19/31)						
0'	1	100	100	0 115		Control
30'						Quinidine 2 mg
31'	2	130	130	0 100		Digitalis at 40 and 301 minutes
316'	9a	134	160			Ventricular tachycardia
320'						Quinidine 2 mg
320'5"	9b	90	100			Sinus rhythm with frequent ventricular
						presystolic contraction and dropped beats
320'15"	9c	166	166			A V dissociation, ventricle responds to
						A V node
320'25"	9d	210	210	0 100		Sinus rhythm
321'	9e					Rhythm alternates between that of
						9c and 9d
322'	10	90	82	0 12 0 20		Sinus rhythm, occasional dropped beat
323'	11	120	130	0 12 0 20		Sinus rhythm with ventricular premature
						contraction
357'	12a	166	200			Ventricular tachycardia
359'						Quinidine 2 mg
360'	12b	220	220	0 12		Sinus rhythm
360'30"	12c	180	180	0 12		Sinus rhythm with frequent ventricular
						premature contraction
Experiment J 2 (5/20/31)						
0'	15a	165	180			Ventricular tachycardia
0'10"						Quinidine 2 mg
0'30"	15b	220	220	0 16		Sinus rhythm
1'	15c		185			Ventricular tachycardia
10'	16a		190			Ventricular tachycardia
10'30"						Quinidine 2 mg
11'	16b	220	220	0 16		Sinus rhythm
13'	16c		220			Ventricular tachycardia
Experiment J 3 (5/26/31)						
0'	1	128	128	0 110		Control, sinus rhythm
						Digitalis at 2, 14 and 22 minutes, sinus slowing
						to 100 and partial A V block before ven-
48'	8a		250			tricular tachycardia
48'10"						Ventricular tachycardia
49'	8b		250			Quinidine 2 mg
50'	8c		250			Ventricular tachycardia
73'						Ventricular tachycardia
						Convulsion death
Experiment V 2						
0'	1	110	110	0 090		Control, digitalis at intervals from 1 to
						237 minutes
237'	9	214	130	0 160		Dropped beats
238'	10		210			Ventricular tachycardia
241'	11	214	A			Standstill immediately after needle was
						inserted into vein, lasted 30 seconds
247'	11c		190			convulsion
247'10"	11d	200 A	A			Ventricular tachycardia
						Standstill lasting about 75 seconds, due to
250'	11e	214	200			insertion of needle, convulsions
250' 5"						Ventricular tachycardia
250'10"	13c	188	A			Quinidine 5 mg
						Ventricular standstill lasting 30 seconds,
						the last portion showing ventricular
250'15"	13d		210			fibrillation convulsion
251'	13e	A	A			Ventricular tachycardia
						Asystole of auricle and ventricle for 15
264'	14a		180			seconds
264' 5"						Ventricular tachycardia
264'10"	14c	214 A	A			Quinidine 5 mg
						Standstill for 65 seconds, auricle stopping
						10 seconds after ventricle, respiration
						ceased temporarily, convulsion

TABLE 1—Abridged Protocols of the Experiments—Continued

Time	Tracing	Rate		P R Interval	Comment
Content	V 2—Continued	Auricle	Ventricle		
4/10'	16b		180		Ventricular tachycardia
80'	17a		180		Physiologic sodium chloride, 57 cc
93'			160		Ventricular tachycardia
355/30"	17b		140		Quinidine 2 mg
303'	17d	188 A	A		Ventricular tachycardia
					Convulsion, respiration ceased, death
Experiment W 2					
0'	1	80	180	0 10	Digitalis at 29 and 57 minutes
78'	5a	88	210		Ventricular tachycardia
78' 5"					Quinidine 2 mg
78'25"	5d	200	200	0 10 0 16	Sinus rhythm
79'30"	5f	170	170	0 10 0 16	Sinus rhythm
92'	7a	200	210		Ventricular tachycardia reappeared at 80 minutes
92' 5"					Quinidine 5 mg
92'10"	7b	188	170		Ventricular tachycardia
94'30"	8	240	120	0 24	Sinus rhythm with 2:1 block, ectopic beats reappeared in 3 minutes
198'	12a	214	190		Ventricular tachycardia
198' 5"					Quinidine 5 mg
198'10"	12b	200	170		Ventricular tachycardia
199'	12c	214	200		Ventricular tachycardia
214'30"					Quinidine 5 mg
222'30"	15a		200		Ventricular tachycardia
222'40"					Quinidine 10 mg
223'	15b		200		Ventricular tachycardia, change in form of Q R S
235'	18a		170		Ventricular tachycardia, multiple Q R S forms
235'10"					Quinidine 10 mg
235'15"	18b	160	100		Ventricular tachycardia
235'20"	18c	A	A		Standstill lasting 15 seconds, convulsion during this period
238'	18d	A	80		Idioventricular rhythm
245'					Quinidine 10 mg, clonic convulsions
252'	19		160		Ventricular tachycardia
Experiment Q 1 (6/3/31)					
98'	10	210	120	0 18	Double vagotomy 2 hours previously, digitalis at 0, 51 and 96 minutes
110'	12a	210	200		Sinus rhythm with dropped beats and ventricular premature contraction
110' 5"					Ventricular tachycardia
110'25"	12b	210	80		Quinidine 2 mg
163'45"	16a	210	120		A V dissociation, ventricle now responds to A V node
163'55"					A V dissociation as in 12b, reappearance of some Q R S groups of 12a
165'25"	16b	210	120		Quinidine 2 mg
165'35"					A V dissociation as in 12b, disappearance of Q R S groups of 12a
165'37"	16c	170	170	0 18	Sinus rhythm lasting 40 seconds
211'45"	19	210	60		A V dissociation, Q R S groups of type in 12b
Experiment S					
					Double vagotomy 2 hours previously, digitalis at 30 minutes and at 73 minutes, 30 seconds
109'30"	4a	214	230		Ventricular tachycardia
109'40"					Quinidine 2 mg
110'10"	4b		180		Ventricular tachycardia
147'	5a	230	220		Ventricular tachycardia
147' 5"					Quinidine 1 mg
147'25"	5b	230	220		Ventricular tachycardia
150'	6a		230		Ventricular tachycardia
150' 8"					Quinidine 3 mg
150'18"	6b		190		Ventricular tachycardia
150'33"	6c		140		Ventricular tachycardia
150'37"	6d	214 A	1		Standstill of ventricle for 15 seconds and of auricle for 7 seconds, convulsion
150'52"	6e		170		Ventricular tachycardia
157'	6f		160		Ventricular tachycardia
Experiment R 1 (6/17/31)					
79'	9a	190	220	0 12	Double vagotomy 2 hours previously, digitalis at 33 and 60 minutes
79'10'					Ventricular tachycardia interrupted by an occasional normal beat
79'45"	9b	180	180	0 12	Quinidine 2 mg
					Fewer ectopic beats

TABLE 1—*Abridged Protocols of the Experiments—Continued*

Time	Tracing	Rate		P R Inter val	Comment
		Auricle	Ventricle		
Experiment R 1—Continued					
88'	10	190	190	0 12	Sinus rhythm
100'	11	200	200	0 14	Sinus rhythm
110'	12	200	200	0 16	Numerous ectopic beats appear
125'	13	200	140	0 17	Sinus rhythm with dropped beats
160'	15	200	140	0 17	Same as 13
Experiment R 2 (6/18/31)					
49'	18	170	215		Digitalis at 20 minutes
64'	19a	190	115		Ventricular tachycardia
64'11"					Ventricular tachycardia
64'41"	20b	190	200		Quinidine 4 mg
69'	21a	190	210		Ventricular tachycardia
69'11"					Ventricular tachycardia
69'36"	21b		175		Quinidine 8 mg
72'	22a		200		Ventricular tachycardia
72'20"					Ventricular tachycardia
72'30"	22i	A	160 A		Quinidine 16 mg
					Ventricular tachycardia, cardiac standstill for 25 seconds, only 82 ventricular beats of various foci in following 3 minutes
78'30"	23	120	120		several convulsions
					A V dissociation, ventricle irregular and QRS groups of varying forms tonic convulsion
81'					Tonic convulsion
83'	24		180		Ventricular tachycardia
238'	26a	166	190		Ventricular tachycardia
238'16"					Quinidine 12 mg
238'26"	26b		150		Ventricular tachycardia in next 4 minutes, A V dissociation with periods of auricular asystole, auricular rates at 90 and ventricular rates from 30 to 140, brief periods of these phenomena alternating
247'	27		155		Ventricular tachycardia
251'	28		150		Ventricular tachycardia
263'	29	A	90		A V dissociation, beats of different foci

electrocardiographic changes which have been observed, some of them having occurred under conditions that make a satisfactory interpretation impossible. The following are the essential changes produced by the injection of quinidine in the course of these experiments:

- 1 Tonic convulsions due to ventricular standstill (chart 1A, tracing 24d)
- 2 Slowing of the ventricular tachycardia (chart 1B, tracings 10a and 10b)
- 3 Disappearance of the ventricular tachycardia followed by a normal sinus rhythm that was slower than the ectopic rhythm (chart 1C, tracings 5b and 5f, chart 2A, tracings 10 and 13)
- 4 Disappearance of the ventricular tachycardia followed by a normal sinus rhythm that was faster than the ectopic rhythm (chart 2A, tracings 10 and 11)
- 5 Disappearance of the ventricular tachycardia followed by A-V dissociation in which the ventricle responded to the A-V node (chart 2B, tracings 12a and 12b)
- 6 Disappearance of the ventricular tachycardia, followed by a slow idioventricular rhythm which was usually very irregular (chart 1A, tracings 24b and 24c, chart 2C, tracings 22 and 23)
- 7 Changes in the forms and duration of the Q-R-S groups (chart 2C, tracings 21b and 22)
- 8 Acceleration, slowing or asystole of the auricle (chart 1A, tracing 24b, chart 2A, tracings 11 and 13)

*Convulsions*—Large doses of digitalis rapidly injected intravenously in the dog may produce a temporary ventricular standstill or marked

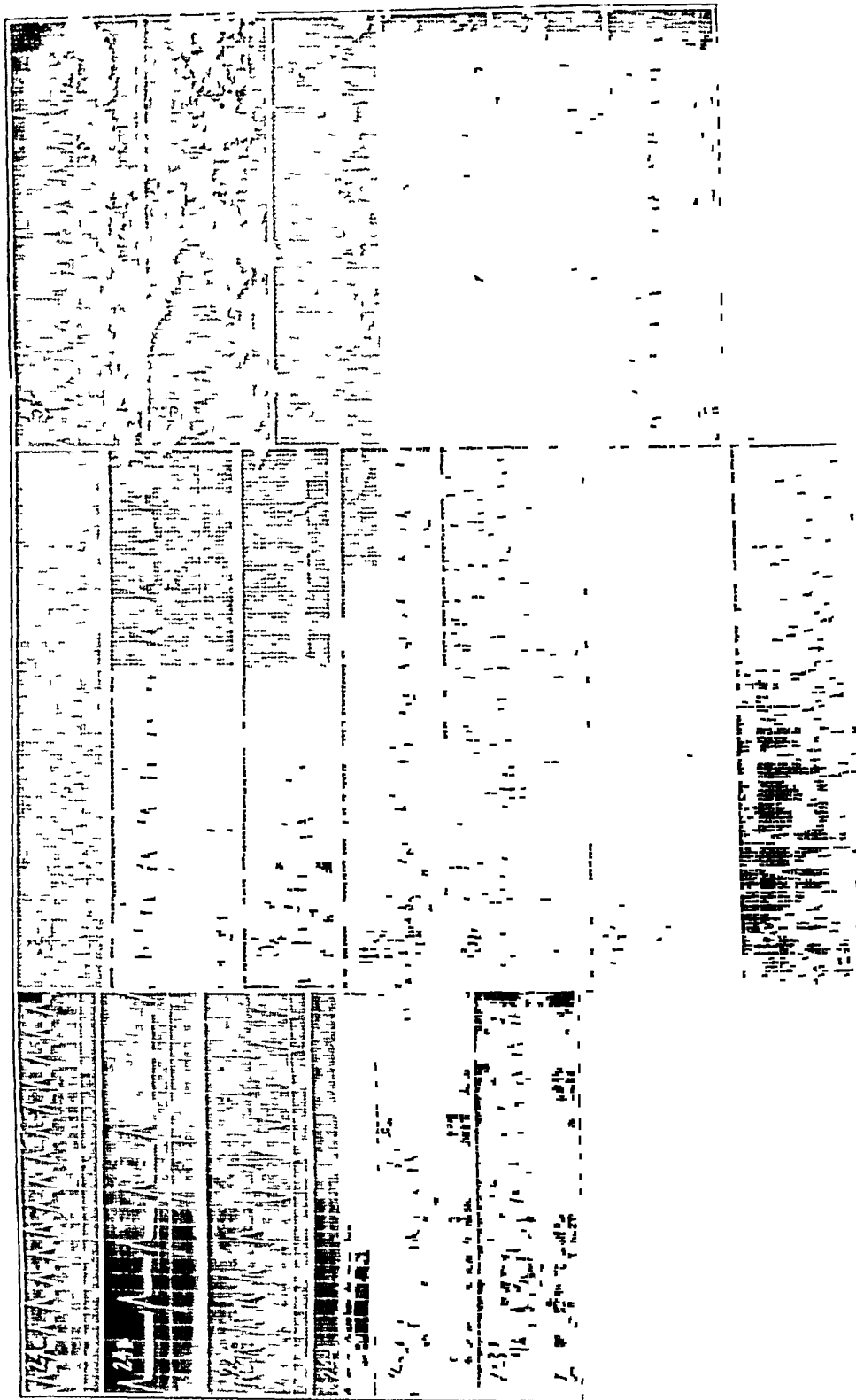


Chart 1—A, selected tracings from experiment T-2 257 minutes, (24a), ventricular tachycardia, rate 200, 257 minutes and 35 seconds (24b), immediately after 5 mg of quinidine, ventricular rate 80, 257 minutes and 40 seconds, (24c), ventricular rate 150, 257 minutes and 50 seconds (24d), ventricular asystole, auricular rate 200, 258 minutes (24e), ventricular rate 90, auricular rate 214, 259 minutes and 30 seconds (24f), ventricular rate 170 B, selected tracings from experiment N 214 minutes and 30 seconds (3b), sinus rhythm, rate 160, 236 minutes and 15 seconds (10a), 4 minutes after digitalis, ventricular rate 160, 236 minutes and 40 seconds (10b), 10 seconds after 5 mg of quinidine, ventricular rate 125, 237 minutes and 30 seconds (10c), rate 150, 273 minutes, (15a), ventricular rate 220, 273 minutes and 20 seconds (15b), 10 seconds after 10 mg of quinidine, 274 minutes (15c), ventricular rate 150 C, selected tracings from experiment W-2 78 minutes (5b), ventricular rate 210, auricular rate 188, 78 minutes and 20 seconds (5c), 20 seconds after 2 mg of quinidine, ventricular rate 210, 78 minutes and 25 seconds (5d), rate 200, 78 minutes and 45 seconds (5e), rate 190, 79 minutes and 30 seconds (5f) rate 170 92 minutes (7a) ventricular rate 210 auricular



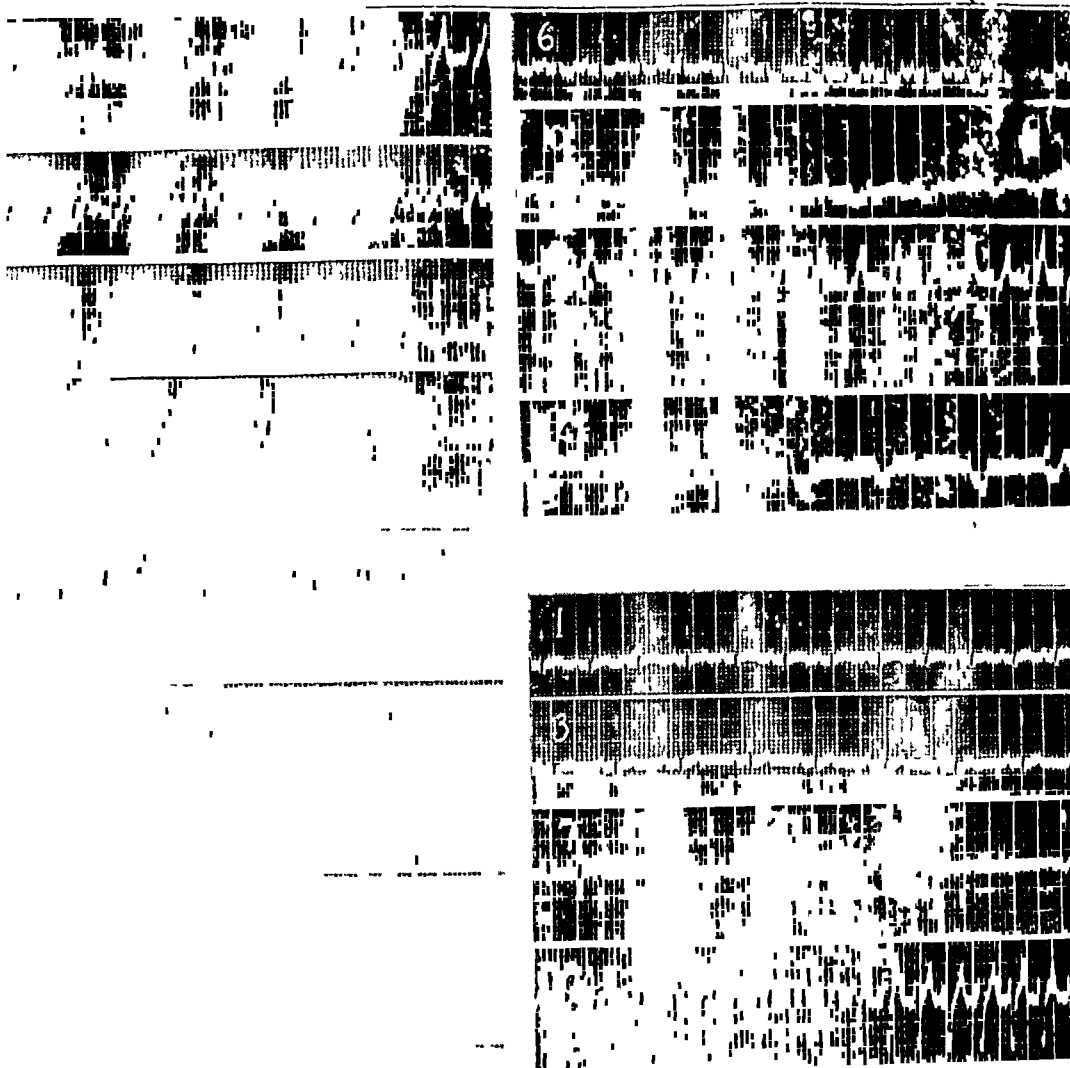


Chart 2—*A*, selected tracings from experiment P-1 91 minutes (10), ventricular rate 190, auricular rate 188, 94 minutes (11), 25 seconds after 4 mg of quinidine, heart rate 200, 98 minutes (12), heart rate 180, 101 minutes and 30 seconds (13), heart rate 150, premature beats *B*, selected tracings from experiment Q-1 75 minutes (6), after digitalis, 112 minutes (10), after additional digitalis, 133 minutes (12a), ventricular rate 200, auricular rate 210, 133 minutes and 30 seconds (12b), 25 seconds after 2 mg of quinidine, ventricular rate 120, auricular rate 214 *C*, selected tracings from experiment R-2 69 minutes (21a), ventricular rate 210, auricular rate 190, 69 minutes and 36 seconds (21b), ventricular rate 175, after second dose of quinidine, 72 minutes and 30 seconds (22), after third dose of quinidine, 78 minutes and 30 seconds (23), only 82 ventricular beats in three minutes *D*, selected tracings from experiment P-1 0 minutes (1), normal sinus rhythm, rate 130, 38 minutes (3), 23 minutes after 0.5 cat unit of digitalis, rate 110, 79 minutes and 30 seconds (7), after additional 0.4 cat unit of digitalis, 86 minutes (8a), ventricular tachycardia, ventricular rate 260

ventricular slowing with irregularities in rhythm, these being attended frequently by a severe systemic disturbance (wild agitation, crying, respiratory distress). Such symptoms usually pass off in from five to ten minutes, and the cardiac slowing is followed by ventricular tachycardia (chart 2D). In the normal dog digitalis in fatal doses causes asphyxial convulsions of a tetanic type owing to circulatory failure ensuing from the ventricular fibrillation. Under certain conditions a reflex may cause sudden standstill of the heart in which digitalis has produced a ventricular tachycardia, although the latter rhythm alone usually results from only 60 or 70 per cent of the fatal dose. Such a reflex standstill may last long enough to cause death in the partially poisoned heart. A reaction much like this was observed in one of the animals in the present series of experiments (experiment V-2). This animal received a total of 15 cat units of digitalis per kilogram in a period of about four hours. Eight minutes after a ventricular tachycardia was induced, the insertion of the hypodermic needle of the syringe containing the quinidine was followed promptly by ventricular asystole lasting thirty seconds, the auricle during this period continuing at a rate of 214 per minute. Quinidine had not been injected. This procedure was repeated six minutes later and was followed by a similar result, sudden ventricular standstill lasting seventy-five seconds, the auricle ceasing to beat about ten seconds after the ventricle and resuming its beat about twenty-five seconds before the ventricle. Subsequently this effect could not be elicited by the reflex or by the injection of salt solution, but was repeatedly produced by small doses of quinidine. In another experiment, which is not included in the tables, and in which ventricular tachycardia was induced by digitalis, the application of a sponge containing amyl nitrite to the nose caused prompt disappearance of the ectopic rhythm followed by a period of complete asystole. That this was also probably due to a reflex rather than to the direct action of the amyl nitrite on the heart was in evidence from the fact that much more intense action after several minutes of inhalation of amyl nitrite did not again abolish the ventricular tachycardia. As already stated, however, ventricular standstill is not the usual mode of death in the dog and in almost all cases in which digitalis in a fatal dose is injected intravenously in a short period of time and a ventricular tachycardia is produced, death results from ventricular fibrillation and is attended by an asphyxial convulsion. Similar results with digitalis were obtained by Rothberger and Winterberg,<sup>6</sup> who reported that with rapid poisoning death occurred as the result of ventricular fibrillation, while with slower poisoning cardiac standstill was produced.

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<sup>6</sup> Rothberger, C. J., and Winterberg, H. Ueber den Einfluss von Strophanthin auf die Reizbildungsfähigkeit der automatischen Zentren des Herzens, *Arch f d ges Physiol* **150** 217, 1913.

It was shown in the previous study<sup>3</sup> that quinidine induces clonic convulsions in the normal dog. This resulted in every instance after total doses of from 21 to 40 mg. It was in no case associated with any disturbance in cardiac rhythm. The convulsant action of quinidine is probably directly on the central nervous system.

In the digitalized dog quinidine produces two types of convulsions. Those occurring with smaller doses are not clonic but tonic. They are not due to direct action on the central nervous system but to cardiac standstill. They occurred in five of seven dogs (V-2, W-2, R-2, S and N), when the ventricular asystole lasted from about fifteen to sixty-five seconds. In two instances (P-2 and T-2) in which the asystole was of shorter duration, about five seconds, there was no change in the respiration or any other external manifestation indicating a cardiac disturbance. Whereas the smallest dose that induced convulsions in the normal animal was 21 mg, doses as small as 5 or 6 mg of quinidine sufficed to cause a tonic convulsion during digitalis poisoning. The contrast between the results following quinidine alone<sup>3</sup> and those after quinidine during digitalis poisoning were striking in the animals of experiments V-2 and W-2. In the animal of experiment V-2, 30 mg of quinidine given in a period of thirty-four minutes induced clonic convulsions, four days later (after all the quinidine had been excreted), in the presence of ventricular tachycardia induced by digitalis, as small a dose as 5 mg of quinidine caused tonic convulsions due to cardiac standstill. Similarly in the animal of experiment W-2, 40 mg of quinidine alone given in a period of thirty-two minutes induced clonic convulsions, six days later, in the presence of ventricular tachycardia produced by digitalis, 30 mg of quinidine given in thirty-seven minutes caused tonic convulsions due to cardiac standstill.

Clonic convulsions of the type occurring in normal animals after quinidine were seen in only one experiment in the digitalized dogs (experiment W-2). In this case a tonic convulsion due to cardiac standstill occurred after 30 mg<sup>7</sup> had been injected in thirty-seven minutes, and a series of clonic convulsions after an additional 10 mg given ten minutes later. The latter convulsions were not attended by ventricular asystole, and it is possible that the impulses discharged during the violent convulsions excited the ventricle to prevent standstill, which might have occurred after this additional dose. The failure to produce the clonic convulsions more often in this series was probably due to inadequate dosage effective at the same time, the interval between the last two fractions being too long, even in those cases in which the total quantity injected corresponded to the convulsant doses.

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<sup>7</sup> The additional doses of quinidine seen in table 1, experiment W-2, are not included because of the long interval intervening.

given to normal animals. It is probable that the digitalis poisoning does not appreciably change the response of the animal to the convulsant action of quinidine on the central nervous system. In the one (experiment W-2) in which clonic convulsions occurred, the total dose of 40 mg<sup>8</sup> in about forty-five minutes was similar to that necessary in normal animals.

*Effect on Rate and Rhythm of the Ventricle*—Some of the studies on the combined actions of digitalis and quinidine were carried out without electrocardiographic tracings. Estimations of the beneficial or injurious effects were made from myocardiographic and carotid blood pressure curves, the essential records being a change in the rate or regularity of the deflections. A change in the rate or regularity of rhythm is, however, no guide as to the nature of the change in the cardiac mechanism produced by quinidine. For example, it was frequently found that a regular rhythm during digitalis poisoning was replaced by an irregular rhythm after quinidine. This might have appeared as an undesirable change in a carotid pressure curve, yet in the electrocardiogram this was often found to be due to change from a regular ventricular tachycardia, which is an advanced toxic rhythm, to regular sinus rhythm with ventricular premature contractions (chart 2A, tracings 10 and 13). A few examples may be mentioned of the numerous combinations of changes in the rate and rhythm in relation to changes in the cardiac mechanism that occurred during the course of the experiments. In experiment W-2 an irregular rhythm became regular and slower, while at another time the reverse occurred, a regular rhythm becoming irregular and slower, yet in both cases the mechanism remained a ventricular tachycardia. In other instances a rhythm remained regular as before, although an important change in the mechanism had taken place, a ventricular tachycardia having been abolished and replaced by a normal sinus rhythm, the latter being attended either by a negligible change in the rate (experiment P-1, chart 2A), or by marked slowing (experiment W-2) or marked acceleration of the cardiac rate (experiment J-1).

*Slowing of the Ventricular Tachycardia*—One of the most constant effects following the administration of quinidine after digitalis had produced a ventricular tachycardia was a reduction in the rate of the ectopic rhythm. This occurred after each of twenty-seven injections of quinidine in ten animals, and after initial doses of as little as from 1 to 5 mg. An average rate of the ventricular tachycardia of 206 per minute was reduced to one of 154 per minute, an average slowing, therefore, of 52 beats per minute, based on the results obtained in different

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8 Only 40 mg. is regarded as the effective dose in this case because more than two hours had elapsed since the previous doses were given.

animals after varying doses of digitalis and quinidine. The amount of slowing in different cases varied widely, between 10 and 130 beats per minute. The striking differences between the changes in the ventricular rate produced by quinidine before and after digitalis in the same animals are shown in table 2, in which comparable sections of the two sets of experiments are brought together.

In several instances the ventricular tachycardia slowed progressively with marked changes in the forms of the Q-R-S groups resulting in idioventricular rhythms with rates of 70 or 80 a minute, or slower, and usually attended by marked irregularity in the rhythm of the ventricle (chart 1A, tracings 24b and 24c, chart 2C, tracings 22 and 23). In most cases, however, the slowing was followed by an abrupt cessation of the ventricular tachycardia with the establishment of one of several

TABLE 2—*Comparison of the Effects of Similar Doses of Quinidine on the Ventricular Rate Before Digitalis and After Digitalis Had Induced Ventricular Tachycardia in the Same Animals\**

Experiment	Before Digitalis			After Digitalis		
	Dose of Quinidine, Mg	Change in Rate		Dose of Quinidine, Mg	Change in Rate of Ventricular Tachycardia	
		From	To		From	To
J 1	2	100	130	2	160	100† 210
T 1, 2	17†	140	230	15†	240	130
W 1, 2	30†	120	170	30†	190	100 standstill
V 1, 2	10	125	180	10	200	180-standstill

\* The rate of the ventricle before the digitalis is in response to the auricle (normal sinus rhythm), while after digitalis there is a ventricular tachycardia (A-V dissociation).

† These doses were given in fractions. The intervals between the fractions are given in table 1 of this paper in the case of the digitalized dogs, and in the previous study<sup>3</sup> in the case of the normal dogs.

‡ The rate of 100 in this case was a sinus rhythm with frequent ventricular premature beats, which was followed by a sinus tachycardia.

new temporary mechanisms: ventricular asystole, normal sinus rhythm or nodal rhythm. In only one instance was quinidine followed by ventricular fibrillation, this occurred in experiment V-2 after ventricular standstill for about fifteen seconds. This is the animal which had received a very large dose of digitalis (1.5 cat units per kilogram) and in which the insertion of the needle into the vein was followed by periods of auricular and ventricular asystole.

**Ventricular Asystole**—In seven of ten animals the disappearance of the ventricular tachycardia was followed by a standstill of the ventricle for periods varying from five to sixty-five seconds in duration and attended in most cases by asphyxial convulsions. The ventricular standstill was often followed by a short period of ventricular tachycardia, which terminated spontaneously in another period of asystole. For example, in experiment V-2 (table 1, tracings 13a, 13c, 13d and 13e) a dose of 5 mg. of quinidine induced a period of asystole lasting thirty

seconds, which was followed by a period of ventricular tachycardia lasting twenty-five seconds, the latter in turn being followed by a second period of asystole lasting fifteen seconds. In some experiments evidence of marked fatigability of intraventricular conduction followed the disappearance of the ventricular tachycardia, as seen from the progressive prolongation of the Q-R-S time from beat to beat (chart 2C, tracing 22). The significance of these observations will be considered later.

In the cases in which the ventricular tachycardia was followed by asystole the final rate of the ventricle before the standstill varied from 100 to 185 in different experiments, but there appeared to be a fairly fixed final rate before its abrupt cessation in the same animal at different times and with different doses of quinidine. This fact is strikingly illustrated in experiments N and V-2. In experiment N after 5 mg of quinidine, the ventricular tachycardia of 160 slowed to 125 per minute, after which it terminated abruptly, about an hour later, after 10 mg of quinidine, a ventricular tachycardia of 220 also terminated abruptly, the final rate again being 125 a minute (chart 1B). In experiment V-2, the ventricular asystole appeared in each of four instances when the rate of the tachycardia was diminished to about 185 per minute. This effect was due to 5 and 10 mg doses of quinidine respectively, in two instances, and to a reflex action in two others. The fifth period of asystole, during which the animal died, was preceded by a ventricular tachycardia with a rate as low as 140 a minute. This reduction in rate occurred about forty-five minutes after the previous effects and was probably due to the changes induced in the heart by the previous repeated and prolonged periods of cardiac standstill.

*Restoration of a Sinus Rhythm*—A normal sinus rhythm was produced by each of nine injections of quinidine in six animals. In eight instances a ventricular tachycardia was thereby abolished, in one, a nodal tachycardia (experiment Q-1). The rate of the new rhythm was extremely variable, in some cases slower and in some faster than the one it replaced, both rhythms being occasionally seen in the same animal after one dose. At least two factors, therefore, may play a rôle in the establishment of a normal sinus rhythm by quinidine, namely, sinus acceleration (probably owing to depression of the vagus) and direct slowing of the ventricular ectopic rhythm, these two frequently taking part at the same time. There are cases, however, in which the main action is sinus acceleration, and in these the abolition of the idioventricular tachycardia may be more apparent than real, the faster sinus becoming the pacemaker and simply masking the rapid rhythm of the ventricle poisoned by digitalis (after 2 mg of quinidine in experiment J-2). The action of quinidine in such a case may be essentially similar

to that of atropine (experiment P-1) In other cases sinus acceleration does not play an important part in the establishment of a normal rhythm because the latter is slower than the rhythm which it has replaced The part played by the direct action of quinidine on the ventricle in the reestablishment of the normal rhythm is more clearly in evidence in the vagotomized animals in which sinus acceleration is sometimes not so prominent a factor (experiment R-1)

The dose of quinidine that sufficed to induce a normal sinus rhythm was very small, 2 mg being effective in six of nine injections, and the largest effective dose being 5 mg When such doses failed to induce a sinus rhythm, larger doses were also ineffective This is due to the fact that in the latter cases digitalis had induced an A-V block<sup>9</sup> in addition to the ventricular tachycardia, so that a normal sinus rhythm was no longer possible even though acceleration of the auricle had occurred, and now the only action of quinidine that could influence the rate and rhythm of the ventricle was the action directly on the ventricle This is found in several experiments, but is especially well illustrated by repeated doses in experiment W-2 Thus a dose of 2 mg established a normal sinus rhythm with a P-R interval that had increased from a normal of 0.10 second before the digitalis to 0.16 second, during the following fourteen minutes, after the intensity of digitalis action had increased, a dose of 5 mg again abolished a ventricular tachycardia and reestablished a sinus rhythm, but there was now a higher degree of A-V block (P-R 0.28, and 2:1 rhythm), after an interval of one hundred and six minutes, the tracing showed definite evidence of complete A-V block (auricular rate 215, ventricular tachycardia 190), and at this time a dose of 5 mg simply slowed the ventricular tachycardia, but in the presence of the complete block failed to reestablish a sinus rhythm

*Effect on the Auricle*—In most instances the rapid ventricular rate masked the P waves, so that the rate of the auricle could not be ascertained An examination of table 1, however, shows that in several cases in which the changes in the rate of the auricle could be followed, quinidine in the overdigitalized heart produced either acceleration or slowing or standstill of the auricle There was no strict parallelism between the changes in the ventricular and auricular rates In the cases in which small doses of quinidine were used, there was an indication that the ventricular tachycardia was more sensitive than the auricular tachycardia to the direct depressant action of the drug, although this may be more

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<sup>9</sup> The larger doses of quinidine might conceivably have contributed to the depression of conduction in the digitalized dog as it did in the experiments of Lewis and others under other conditions, although in the normal dog, depression of A-V conduction was never seen after quinidine in our experiments

apparent than real in some cases, because direct depressant action on the sinus may be masked by simultaneous depression of the vagus. Nevertheless, in some instances a considerable effect on the ventricle was in evidence when no effect on the auricular rate could be detected, while the reverse was not seen, in experiment N (tracing 14*b*), a 5 mg dose of quinidine slowed the ventricular tachycardia from 190 to 160, while the rate of the auricle remained at 190 a minute, in experiment P-2 (tracings 8*b* and 8*d*), the last dose of 4 mg of quinidine produced complete standstill of the ventricle with no appreciable change in the auricular rate of 250 per minute. This was also seen in experiment Q-1 (tracing 12*b*), in which the vagi were excluded by vagotomy, a 2 mg dose of quinidine abolished the ventricular tachycardia, while no influ-

TABLE 3—Comparison of Normal and Digitalized Dogs with Reference to Changes in the Auricular Rate Following the Administration of Quinidine

Experiment	Normal Dog			Digitalized Dog		
	Dose of Quinidine, Mg	Change in Rate		Dose of Quinidine, Mg	Change in Rate	
		From	To		From	To
Q 1 (vagotomized)				2	210	170
R 2 (vagotomized)				28*	190	Standstill
S (vagotomized)				3	214	Standstill
Y 1 (vagotomized)	2	210	230			
X 1 (vagotomized)	27*	150	193			
Z (vagotomized)	5	160	120			
N 2				{ 5	?	Standstill
J 1	2	100	130	{ 20	190	Standstill
T 1, 2	5	138	190	2	134	90
V 1, 2	10	125	180	5	210	Standstill
W 1, 2	40*	160	210	10*	214	Standstill
				37*	214	Standstill

\* These were injected in fractional doses. The exact intervals between doses are given in table 1. The table does not give all the results obtained in normal animals,<sup>3</sup> but only selected experiments with comparable doses of quinidine, which emphasizes the difference between the type of reactions seen in normal and in digitalized animals.

ence on the auricular rate of 210 was in evidence. At other times the changes in the auricle and ventricle ran parallel. The larger doses which caused ventricular asystole usually caused auricular asystole as well, thus, in experiment N (tracing 15*b*) a dose of 10 mg of quinidine caused slowing of the auricle and ventricle which terminated in complete standstill of both. Frequently, the change in the rate of the auricle ran in a direction opposite to that of the ventricle, the auricle being accelerated, owing to depression of the vagi, and the ventricular tachycardia slowed, owing to direct action on the ventricle (experiment P-1, tracings 9*b*, 11 and 13). This was frequently the mode by which a normal sinus rhythm was reestablished.

An interesting aspect of the auricular response to quinidine in the digitalized animal is the slowing and complete standstill of the auricle. The standstill of the auricle, like that of the ventricle, is also usually abrupt after an initial period of slowing. Sometimes the auricular



deflections cease without any appreciable previous slowing. These changes have been tabulated in table 3 and for emphasis are compared with the usual type of response in normal animals. In the previous study<sup>3</sup> it was shown that sinus acceleration occurred invariably after quinidine in the normal animal, and that in only three of twelve experiments was momentary and moderate slowing observed. Auricular standstill never occurred in the normal animal even after very large doses of quinidine, whereas during the action of digitalis auricular standstill appeared in seven of ten animals, in some after very small doses of quinidine, from 3 to 5 mg. The differences in the response were particularly striking in the four cases (J-1, T-2, V-2 and W-2) in which comparable doses of quinidine were given to the same animals before and after digitalis. The possibility suggested itself that the standstill of the auricle might not be a direct effect of quinidine on the auricle but rather a secondary effect of the ventricular standstill. An examination of the records, however, shows that while in several instances the auricle stopped after the ventricular arrest appeared, there was no fixed order in which the two chambers came to a standstill, in some, asystole appeared in the two at the same time (experiment V-2, tracing 17*d*), in others only the ventricle stopped, or stopped first (experiment N, tracing 15*b*), in still others the auricle was in asystole while the ventricle was beating (experiment W-2, tracing 18*d*).

*Effect on A-V and Intraventricular Conduction*—In the previous study<sup>3</sup> it was shown that quinidine depresses intraventricular conduction but does not prolong A-V conduction in the normal unanesthetized dog. Lewis and his co-workers,<sup>10</sup> using fully anesthetized dogs with the thoracic cavity open, found that similar doses of quinidine caused not only prolonged intraventricular, but also markedly impaired A-V conduction. It is clear, therefore, that with a change in the conditions of the experiment, perhaps in this case due to the anesthesia and low blood pressure, quinidine gives different results. We have already shown that digitalis poisoning renders both the auricle (or sinus) and ventricle more susceptible to the depressant action of quinidine so that slowing which is rarely seen in the normal dog becomes the most prominent effect of quinidine during the action of digitalis. Our records have been analyzed for evidence of any effect of quinidine on the P-R intervals in the digitalized dogs. The material was not entirely satisfactory for this purpose for several reasons. In most instances a ventricular tachycardia was induced with digitalis before the quinidine was injected, hence under those conditions A-V conduction time could not be ascer-

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10 Lewis, T., Drury, A. N., Ilescu, C. C., and Wedd, A. M. Observations Relating to the Action of Quinidine upon the Dog's Heart, with Special Reference to Its Action on Clinical Fibrillation of the Auricles, *Heart* 9:55, 1921.

tained. In many cases digitalis induced varying degrees of heart block which became more intense during the course of the experiment, and when a greater degree of A-V block was present after quinidine than before, there was no way of knowing whether it was due to digitalis, to quinidine or to both, because a greater degree of block that might have been caused by digitalis would be masked by the ventricular tachycardia and would come into view only when the latter was abolished by the quinidine.

In experiment P-1, quinidine diminished A-V block induced by digitalis. Thus, following the digitalis the sinus rate was slowed and the P-R interval prolonged from 0.12 to 0.16 second, with dropped beats (chart 2D). A dose of 4 mg of quinidine accelerated the heart rate from 100 to 150 and the P-R interval was shortened to 0.10 second. It is probable that in this instance the chief action of digitalis depended on the vagal tone, and the main action of quinidine was through depression of the vagi.

In one vagotomized dog (experiment Q-2) in which digitalis had induced an A-V block without the ventricular tachycardia, quinidine diminished the block by what appears to be still another mechanism. Digitalis had induced a 2:1 block with a P-R interval of 0.18 second (auricular rate 240, ventricular rate 120). About fifteen seconds after the intravenous injection of 4 mg of quinidine the block was temporarily diminished, resulting in a 1:1 rhythm with a P-R interval of 0.18 second, the auricular rate having slowed from 240 to 200 per minute during this action. The reduction in the block in this instance was probably due to the slowing of the auricle as the direct effect of the quinidine. This effect of rate on A-V conduction is in harmony with the observations of Lewis and his co-workers.<sup>10</sup>

Our experiments, therefore, afford no indication that quinidine in small doses directly depresses A-V conduction in the digitalized animal. It is, of course, conceivable that it might under suitable conditions cause depression indirectly, namely, through its parietic action on the vagus which by sinus acceleration might give rise to an impairment of A-V conduction.

The normal sinus rhythm established by quinidine, after the ventricular tachycardia was abolished, frequently showed a longer Q-R-S time than before the ectopic rhythm appeared. Thus in experiment W-2, the interval had increased from 0.03 to 0.05 second after 2 mg of quinidine, in experiment J-1, from 0.03 to 0.04 second after 2 mg and from 0.04 to 0.06 second after an additional 2 mg, in experiment P-1, it increased from 0.04 to 0.06 second after several doses totaling 10 mg. Such marked effects following the 2 mg doses of quinidine were not seen in normal animals, but the difficulties in interpretation are

here much the same as in the case of the P-R intervals, since they may be due to the digitalis action alone on the ventricle, the effect being masked by the ventricular tachycardia, or to the effect of the previous tachycardia itself, as we will show later. These possibilities receive support from the facts that in experiment Q-2, in which ventricular tachycardia did not result from digitalis, two doses of quinidine, 2 and 4 mg respectively, did not prolong the Q-R-S time beyond the control of 0.03 second, and in experiment N, two doses of quinidine, 2 and 5 mg respectively, failed to prolong the Q-R-S time of 0.03 second. In this last experiment, after the action of digitalis became sufficiently intense to produce a ventricular tachycardia, an additional dose of 5 mg of quinidine established a sinus rhythm with a Q-R-S time that had increased from 0.03 to 0.05 second.

We have already stated that quinidine not only slowed the rate of the ventricular ectopic rhythms resulting from digitalis, but frequently produced marked changes in the forms of the Q-R-S groups. As a change in the focus or path of the impulse may alter the Q-R-S time without any direct depression of intraventricular conduction, it was in many cases not possible to ascertain whether such depression had occurred. In several instances, however, the tracing left little doubt that quinidine, even in very small doses, can produce marked depression in intraventricular conduction as measured by the change in the duration of the ectopic Q-R-S groups (chart 2C, tracings 21a, 21b and 22).

*Effect of Vagotomy*—An examination of table 1 shows that after double vagotomy the effects of quinidine on the heart poisoned by digitalis were essentially similar to those in normal digitalized animals. It would be expected that sinus acceleration would not play as important a rôle in the restoration of the normal rhythm in the vagotomized animal, but the experiments are too few to ascertain this fact, and it is probable that even with a larger number of experiments the rôle of the vagi would not be prominent, because, as has been shown in the previous study,<sup>3</sup> the intravenous injection of quinidine may result in considerable acceleration of the sinus rate, even in vagotomized animals.

*Effect of Degree of Digitalization on Response to Quinidine*—The results obtained in the same animal made it possible to study the effects of varying doses of quinidine in different stages of digitalis poisoning. They show in several cases (table 1) that the effects of given doses of quinidine depend on the intensity of digitalis action. Thus in experiment J-1 a 2 mg dose abolished a ventricular tachycardia and reestablished a sinus rhythm after moderate digitalis poisoning, whereas a similar dose of quinidine given several days later

(experiment J-3) after an injection of digitalis that proved to be fatal, produced no effect on the ventricular tachycardia. Similarly, in experiment P-1, a 2 mg dose of quinidine slowed the rate of the ventricular tachycardia (from 260 to 230), whereas the same dose repeated on the following day, after more intense digitalis poisoning, produced no effect (experiment P-2). In experiment N, a 5 mg dose of quinidine, injected less than four minutes after digitalis had produced ventricular tachycardia, slowed the latter from a rate of 160 to one of 125 per minute, which was in turn followed by a normal sinus rhythm. When the action of digitalis became more intense within the next twenty-five minutes as seen by the fact that a ventricular tachycardia with a much higher rate appeared (190 per minute as compared with 160 per minute), the effect of a similar dose of quinidine (5 mg) was less pronounced, it served simply to slow the ventricular tachycardia to 160, but failed to produce a sinus rhythm. At a still later period (sixty-three minutes after the ventricular tachycardia had been induced by digitalis), a dose of 10 mg of quinidine failed to produce any change in the rate of the ventricular tachycardia. The failure of the second 5 mg dose to induce a sinus rhythm was due, as in other cases, to the presence of A-V block, as seen by the fact that the auricular rate was 190 per minute and the ventricle was beating independently at a slower rate of 160. The latter fact is more strikingly brought out by the other observations in this experiment, in that twice the dose of quinidine (10 mg) injected about ten minutes after the second dose of 5 mg served merely to produce ventricular asystole for a period of twenty-four seconds, this having been neither preceded nor followed by a sinus rhythm.

*Duration of Effects of Quinidine*—It is well known that the toxicity of quinine and quinidine varies greatly with the rate of injection because of the rapid excretion. Gordon, Matton and Levine<sup>11</sup> found that the fatal dose of quinidine sulphate in the cat was about 25 mg per kilogram when injected intravenously in a single dose. The dose became 45 mg when injected at the rate of 15 mg every six minutes and 100 mg when given in small doses over two hours. Weiss and Hatcher<sup>12</sup> also found that the dose increased with the period of injection, and that in the cat the essential elimination was practically complete within three to four hours. In the previous study<sup>3</sup> it was shown that the effects of quinidine on the electrocardiogram appeared

11 Gordon, B., Matton, M., and Levine, S. A. The Mechanism of Death from Quinidine and a Method of Resuscitation. An Experimental Study, *J. Clin. Investigation* **1** 497, 1925.

12 Weiss, S., and Hatcher, R. A. Studies on Quinidine, *J. Pharmacol. & Exper. Therap.* **30** 335, 1927.

within a few seconds after the intravenous injection, almost completely disappeared in most cases in less than from five to ten minutes and were rarely in evidence within a half hour following intravenous administration. The duration of the effects produced by the intravenous injection of quinidine on the abnormal rhythms was much more variable than in the normal animal. On the whole the effect was brief, however, lasting in the majority of instances less than three minutes, in some cases up to about ten minutes, while in a few instances considerable effect was still in evidence after from one-half to one and one-half hours (P-2, T-2, Q-1 and R-1). The duration of the effects of quinidine in the digitalized animals does not depend on the elimination of quinidine alone but on at least two other factors, namely, the partial excretion of digitalis during the few hours of the quinidine experiment, and secondly, on the fact that an ectopic rhythm that has been abolished by quinidine may not necessarily reappear when the quinidine has been excreted. For example, it is well known that the circus movement of auricular fibrillation, after having been abolished by quinidine, may remain in abeyance in some cases for several weeks or months without the use of any additional drug—long after the previous doses have been excreted.

It is probable that the dosage of quinidine bears some relation to the duration of some of the effects, but the conditions of our experiments were so exceedingly variable that no correlation could be detected between these two factors. For example, in experiment Q-1 two doses of 2 mg. each abolished a ventricular tachycardia, and marked slowing of the heart was still in evidence ninety minutes following the first dose, whereas in experiment T-2, two doses of 5 and 10 mg., respectively, abolished the ventricular tachycardia, but in this case the effect lasted no longer than two and a half minutes.

#### COMMENT

In the treatment of patients with auricular fibrillation digitalis is usually given to relieve the cardiac failure and quinidine usually to reestablish the normal rhythm. Lewis and his co-workers<sup>13</sup> showed that in those in whom the tendency for digitalis to shorten the refractory time interferes with the action of quinidine, somewhat larger doses of the latter may be necessary to establish the normal rhythm. Viko, Marvin and White<sup>14</sup> were unable to detect any interference with the effectiveness of quinidine in terms of the doses necessary to abolish

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13 Lewis, T., Drury, A. N., Wedd, A. M., and Iliescu, C. C. Observations upon the Action of Certain Drugs upon Fibrillation of the Auricles, *Heart* 9 207, 1922.

14 Viko, L. E., Marvin, H. M., and White, P. D. A Clinical Report on the Use of Quinidin Sulphate, *Arch. Int. Med.* 31 345 (March) 1923.

the circus movement in patients who had been previously digitalized Wolff and White<sup>15</sup> observed that, theoretically, digitalis in suitable doses might favor the restoration of a normal rhythm by quinidine, and were of the opinion that such was the case in a group of their patients, although the very small number of their cases and the slight difference between the two groups seem insufficient to justify the conclusion. They did not observe any undesirable symptoms in patients with auricular fibrillation which they could attribute to the combined action of the two drugs. Levy<sup>16</sup> observed ventricular tachycardia five times after quinidine in a series of twenty-five patients with auricular fibrillation. The procedure prior to quinidine was to restore compensation by various factors in addition to digitalis if necessary. It is possible, therefore, that the ventricular tachycardia may not have been due to quinidine, but to the combined action of large doses of digitalis and quinidine, although Levy ascribed the result to quinidine alone. It is well known,<sup>17</sup> for example, that a potential rapid idioventricular rhythm as the result of digitalis may be held in abeyance by a rapid supra-ventricular pacemaker, and the suppression of such a pacemaker will bring into view a ventricular tachycardia. The latter might therefore be due to the action of digitalis on the ventricle, which would become evident only after quinidine had induced an A-V block or auricular standstill.

In a more recent study of the use of quinidine in chronic auricular fibrillation, Maynard<sup>18</sup> listed, among observations on the toxic effects of quinidine, ventricular premature contractions which occurred in short runs in some patients, an attack of ventricular paroxysmal tachycardia, one case of bigeminal rhythm, and two cases of transient bundle branch block. He found that impaired A-V conduction occurred quite regularly when the normal rhythm was established. All these effects may be produced by digitalis alone, and none of them has been produced by even larger doses of quinidine alone in the normal unanesthetized dog. This is not intended to suggest that quinidine was not directly responsible for the effects in these patients, but to justify the question as to what part the action of digitalis may have played. The paper makes no mention of the use of digitalis in the group of patients as a whole, with the exception of a casual reference to its use in a fatal case, although one would be justified in suspecting—unless the state-

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15 Wolff, L., and White, P. D. Auricular Fibrillation, *Arch Int Med* 43 653 (May) 1929

16 Levy, R. L. Clinical Studies on Quinidine, *New York State J Med* 22 276, 1922

17 Gold, Lieberman and Gelfand<sup>5</sup> Rothberger and Winterberg<sup>6</sup>

18 Maynard, E. P. Five Years' Experience in the Treatment of Chronic Auricular Fibrillation with Quinidine Sulphate, *Am J M Sc* 175 55, 1928

ment is made to the contrary—that of a large group of patients with auricular fibrillation followed for from one to five years, some had received digitalis

There are numerous papers in the literature which bear directly on the same point, but the foregoing few will suffice to illustrate that, in general, insufficient attention has been paid to the matter of previous digitalization in clinical studies of the action of quinidine. The views on the uses and dangers of quinidine during the action of digitalis in man, with the one exception of their combined effect on the fibrillating auricle, are based almost entirely on inferences derived from a rather meager and inadequate experimental literature dealing directly with their combined actions. In many cases they are inferences from effects when the two drugs are used separately. Thus, the fact that quinidine can abolish fibrillation and digitalis can produce it led Frey<sup>19</sup> to advise against their use together in auricular fibrillation, although subsequent investigations left little doubt that this mechanism can be effectively abolished during the full action of digitalis. The same facts led Pezzi and Clerc<sup>20</sup> to recommend the use of quinine during the administration of digitalis in patients with a sinus rhythm to prevent auricular fibrillation, which the latter drug might provoke. They recommended it further to prevent other toxic effects of digitalis such as coupled rhythm and extrasystoles, which they thought might be forerunners of ventricular fibrillation. They stated that they were unable to produce toxic effects with Nativelle's digitalin in dogs which had received quinine, but did not give any details of these experiments.

Schott,<sup>21</sup> in discussing the dangers of quinidine in man, warned against the combination of quinidine and digitalis because both depress A-V conduction, and he used as evidence the fact that conduction was depressed in his experiments with guinea-pigs after massive oral doses, about 1,500 mg of quinidine per kilogram.

Weichmann<sup>22</sup> suggested the use of strophanthin intravenously to overcome the cardiac paralysis in man that may result from acute poisoning by quinidine. He based this suggestion on the results of experiments on the perfused heart of the frog in which, after quinidine had caused standstill, beating was reestablished by the addition

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19 Frey W. Chinidin zur Bekämpfung der absoluten Herzunregelmässigkeit, *Deutsches Arch f klin Med* **136** 70, 1921

20 Pezzi, C, and Clerc, A. Action cardiaque de la quinidine, *Presse med* **28** 334, 1920

21 Schott, E. Zur Frage der Chinidintherapie, *Deutsches Arch f klin Med* **134** 208, 1920

22 Weichmann E. Untersuchungen über das Chinidin, seine Antagonisten und Synergisten, *Klin Wchnschr* **34** 1683, 1922

of strophanthin to the perfusion fluid. Cattell,<sup>23</sup> on the other hand, found that in the perfused frog's heart digitalis did not appear to modify the toxic action of quinidine, although when the order of the poisoning was reversed an antagonism was observed, namely, quinidine helped to revive ventricular contractions after they had practically ceased during the action of digitalis, and previous perfusion with dilute solutions of quinidine caused a delay in the subsequent action of digitalis with respect to the reduction in the amplitude of the contraction.

To elucidate the mechanism by which quinidine produces toxic effects in man, Frey and Hagemann<sup>24</sup> performed experiments on rabbits, from which they concluded that the essential toxic effect is a depression of the heart and that the injection of strophanthin neither prevented nor abolished the effect. Their results, however, have no application to the practical problem because they employed massive doses of both drugs, namely, from 72 to 100 mg of quinidine lactate intravenously, and injections of 1 mg of strophanthin to average sized rabbits.

Haskell<sup>25</sup> obtained interesting results in experiments on dogs, from which he concluded that quinidine may exert a favorable action on the abnormal rhythms induced by digitalis. His animals were anesthetized with such substances as ether, morphine and chlorbutanol, and records were taken with the myocardiograph or carotid blood pressure manometer, while it is true that quinidine was followed by changes in the rate and rhythm of the heart, there was no way, in the absence of electrocardiographic tracings, of ascertaining the mechanism of the heart beat following the quinidine and whether or not the changes were beneficial. The same applies to the study of Jackson, Friedlander and Lawrence,<sup>26</sup> who found that cardiac irregularities induced by digitoxin in dogs disappeared after the injection of quinidine.

Weiss and Hatcher<sup>12</sup> failed to detect synergism or antagonism between quinidine and ouabain in terms of the fatal doses in acute experiments in cats. This observation was made in the course of another study, and was not investigated further.

The present investigation was planned to study primarily the changes in cardiac mechanism under the combined actions of digitalis and

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23 Cattell, M. Observations on the Action of Digitalis on the Frog Heart and Its Modification by Quinidine, *J Pharmacol & Exper Therap* **27** 287, 1926.

24 Frey, W., and Hagemann, E. Klinische und experimentelle Daten über toxische Chinidinwirkung, *Ztschr f d ges exper Med* **25** 290, 1921.

25 Haskell, C. C. The Influence of Quinidine on the Cardiac Irregularity Produced by Digitalis, *J Pharmacol & Exper Therap* **32** 223, 1928.

26 Jackson, D. E., Friedlander, A., and Lawrence, J. V. An Experimental Investigation of the Pharmacological Action of Quinidine, *J Lab & Clin Med* **7** 311, 1922.



quinidine rather than to ascertain any synergism or antagonism between the two drugs in terms of doses that are fatal for normal animals. It appeared to us that the absence of antagonism expressed in terms of fatal doses, as some have found, would not exclude, *a priori*, the possibility of a beneficial action of quinidine in digitalis poisoning that might even avert a fatality resulting indirectly. To illustrate, ventricular tachycardia induced by digitalis in the normal cat or dog is usually not fatal. However, such an extremely rapid ectopic rhythm in the damaged heart of a patient may lead to heart failure and death, the cause of death therefore being the abnormal rhythm rather than direct depression by the drug. Hence in such a case the mere abolition of the ventricular tachycardia by quinidine, if that were possible, might give an indication of an important antagonism to the fatal action of digitalis that would not be in evidence in the normal animal.

The results of the present study show that during the action of digitalis in the normal dog, quinidine produces effects on the auricle and ventricle which may result in an apparently favorable antagonism to the toxic effects of digitalis. Thus, in a case in which the latter has induced a ventricular tachycardia, quinidine may abolish this ectopic rhythm and at the same time slow the sinus, reestablishing a normal sinus rhythm with a rate that is considerably slower than the ectopic rhythm that was abolished. Such an antagonism should prove useful in suitable cases in man. An examination of the details of our results, however, shows further that because of the marked variability in the effects of digitalis and quinidine in varying doses, the combination of actions of quinidine that can prove useful in antagonizing the toxic effects of digitalis is exceedingly difficult to obtain, and that more often the injection of quinidine is followed by effects that are undesirable. In so far, then, as these results have any bearing on the clinical problem, they show that the use of quinidine to abolish the ventricular tachycardia induced by digitalis, while it may occasionally prove effective, presents dangers.

These experiments have, however, brought up certain interesting questions relating to the behavior of the heart under the influence of digitalis and quinidine, and we believe that the results throw light on the mechanism involved in some of the effects of both drugs that on the surface appear somewhat perplexing.

We have shown that digitalis alone causes a ventricular tachycardia and when the latter is abolished the ventricle frequently seems temporarily incapable of automatic activity. This is similar to the behavior of the ventricle after the sudden production of complete heart block<sup>27</sup>

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27 Erlanger, J., and Hirschfelder, A. D. Further Studies on the Physiology of Heart-Block in Mammals, *Am J Physiol* **15** 153, 1906

The marked acceleration of the ventricle which occurs during digitalis poisoning is commonly referred to as an increased rhythmicity. This might be interpreted merely as an increase in the speed of the normal automatic "centers" of the ventricle,<sup>6</sup> while some have regarded the tachycardia as arising from an abnormal mechanism in the ventricle, such as a circus movement.<sup>28</sup> It is possible that the mechanism of the rapid idioventricular rhythm is not the same with different degrees of digitalis poisoning. If it were merely a matter of normal "centers" (those that excite the ventricle in ordinary complete heart block) becoming more active as the result of the digitalis, one would expect that greater difficulty would be encountered in completely suppressing such rhythmic activity than in the case of the normal, slow automaticity of the ventricle. Yet in one of our experiments digitalis produced a ventricular tachycardia of 220 a minute, and a reflex arising from the mere insertion of a needle into the vein promptly slowed and abolished this rhythm and induced a complete standstill of the ventricle for seventy-five seconds. Such is not the behavior of the slow idioventricular rhythm of complete heart block under the usual conditions. The assumption that the ventricular tachycardia induced by digitalis always represents an increase in the rhythmic activity of the normal automatic "centers" of the ventricle leads to the paradoxical conclusion that the greater the rhythmicity of the "center" the more readily is its activity abolished. It seems, therefore more likely that, in many cases at least, it is an abnormal mechanism in the ventricle (produced by digitalis) which drives the latter at this rapid rate. The fact that in our experiments the ectopic rhythm usually disappeared abruptly and the fact that it did so after slowing to a fairly uniform point with varying doses of quinidine are suggestive of the behavior of a circus movement. But whatever the mechanism, the fact remains that during poisoning by digitalis alone, under special conditions these two changes in the ventricle may become evident: (1) An abnormal and exceedingly rapid pacemaker appears, and (2) there is depression of the normal automatic "centers" of the ventricle.

In the presence of A-V block induced by digitalis, doses of quinidine as low as 5 mg sufficed to abolish the ventricular tachycardia, resulting frequently in prolonged periods of ventricular standstill. This action of quinidine was also seen in the animal described, in which the reflex alone was effective, and the results after quinidine in this case were indistinguishable from those produced by the reflex. Following quinidine in the digitalized animal, again two changes in the ventricle

28 (a) Palmer, R. S., and White, P. D. Paroxysmal Ventricular Tachycardia with Rhythmic Alternation in Direction of Ventricular Complexes in the Electrocardiogram, *Am Heart J* **3** 454, 1928. (b) Luten, D. Clinical Studies of Digitalis. III. Advanced Toxic Rhythms, *Arch Int Med* **35** 87 (Jan) 1925.

become manifest (1) abolition of the abnormal mechanism causing the disappearance of the ventricular tachycardia, and (2) depression of the normal automatic "centers" of the ventricle

With respect to the ventricular tachycardia, therefore, quinidine exerts actions antagonistic to those of digitalis, the one abolishing the ectopic rhythm induced by the other. The ventricular standstill, however, that results from the two combinations, digitalis-reflex and digitalis-quinidine, does not lend itself to such a direct explanation. There is no known direct action of toxic doses of digitalis on the mammalian heart that would lead one to infer a direct depressant effect on the automatic activity of the ventricle. As for quinidine alone, there are several studies<sup>29</sup> which show that in the dog this drug does not readily depress this function. When fatal doses of quinidine were given to dogs under ether anesthesia the last signs of cardiac activity consisted in a slow rhythmic beat of the ventricle.<sup>29a</sup> In our own experiments it was a rather striking fact that the standstill of the ventricle after small doses of quinidine lasted no longer than after a sudden reflex stimulus, and after large doses of quinidine it lasted no longer than after small doses of the drug. The reverse would be expected if the standstill resulted from a direct action of the drug on the ventricle. These facts make it impossible to ascribe the ventricular pause to a direct depressant action of digitalis or quinidine on the ventricular rhythmicity without introducing the idea of an unusual type of synergism between the two drugs.

We believe that the explanation of the ventricular standstill is not to be found solely in any direct action of either of the drugs alone or in combination, but rather in certain facts relating to the behavior of the ventricle after rapid excitation that were described many years ago by Erlanger and Hirschfelder<sup>27</sup> and by Cushny<sup>30</sup>. The similarity between the results of Cushny's experiments and ours are extraordinary in view of the totally different conditions under which they were obtained. A close comparison of the details of these experiments leaves little doubt that the two sets of results have the same significance.

Cushny<sup>30</sup> showed that in the perfused heart of the cat and rabbit in which an idioventricular rhythm was established by severing the bundle of His, periods of rapid excitation of the ventricle by electrical shocks so fatigued the automatic activity of the ventricle that, when the external

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29 (a) Cohn, A. E., and Levy, R. L. Experimental Studies of the Pharmacology of Quinidine, *Proc Soc Exper Biol & Med* **18** 283, 1921. (b) Drury, A. N., Horsfall, W. N., and Munly, W. C. Observations Relating to the Action of Quinidine upon the Dog's Heart, the Refractory Period of, and Conduction in, Ventricular Muscle, *Heart* **9** 365, 1922.

30 Cushny, A. R. Stimulation of the Isolated Ventricle, with Special Reference to the Development of Spontaneous Rhythm, *Heart* **3** 257, 1912.

stimuli ceased, periods of ventricular standstill for as long as twenty seconds followed, and that sometimes the resumption of the spontaneous beating was interrupted by additional periods of standstill, indicating that the previous rapid excitation had rendered the automatic function more liable to fatigue. This occurred only when the ventricle was isolated from the impulses coming from the auricle. He showed further that while the period of rapid excitation had depressed conductivity and rhythmicity, the excitability and contractility of those hearts were not depressed because minimal stimuli applied during the pause still elicited a contraction of the ventricle of a magnitude the same as, or even greater than, that before the period of rapid excitation, and when the bundle of His had not been severed, the ventricular pause under the conditions of these experiments failed to occur. Others<sup>31</sup> have also shown that the automaticity can vary independently of the remaining functions of the heart.

As we have already indicated, practically identical results have been obtained in our experiments with the normal unanesthetized dog. The foregoing, therefore, afford a basis for a rational explanation of the effects of quinidine on the ventricle during the tachycardia induced by digitalis without material dependence on assumptions that have not received significant experimental support. Thus, by direct action digitalis induces an abnormal mechanism in the ventricle which drives the latter at a rapid rate in much the same way that electrical stimulation would, and as a result of this rapid excitation, the normal rhythmic "centers" of the ventricle are fatigued. The abolition of the abnormal rapid pacemaker by quinidine sometimes results, after a brief standstill, in a slow automatic rhythm of the ventricle which exhibits considerable fatigability, as shown by the very irregular rhythm and intermittent pauses. At other times ventricular standstill of long duration occurs, the inhibition of ventricular automaticity being due to the previous period of rapid excitation rather than to any direct action of the drugs. That the excitability of the ventricle has not been materially depressed by either of the drugs or by the period of rapid excitation is in evidence from the fact that if supraventricular impulses can reach the ventricle, the latter is capable of responding promptly to such impulses with a rate as rapid as 220 a minute, hence, in the absence of complete heart block, a small dose of quinidine after abolishing the ventricular tachycardia does not produce ventricular standstill but a sinus rhythm.<sup>32</sup>

31 Herring, H. E. Ueber die Unabhängigkeit der Reizbildung und der Reactionsfähigkeit des Herzens, *Arch f d ges Physiol* **143** 370, 1911.

32 Complete cardiac standstill may result, even in the absence of A-V block, if the dose of quinidine has been large enough to cause auricular asystole as well

When death results after the administration of quinidine under such conditions as in these experiments, it is therefore to be ascribed, not to a direct action of the two drugs, but rather to the inhibition of the automatic activity of the ventricle resulting from the rapid idioventricular rhythm induced by digitalis. This distinction is emphasized because it appears to be of more than academic interest. Quinidine has been employed from time to time for abolishing ventricular tachycardia in man arising under various pathologic conditions.<sup>2</sup> Ventricular tachycardia is occasionally produced by the toxic action of digitalis in man.<sup>28b</sup> We have shown that experimentally this toxic rhythm induced by digitalis may be abolished by quinidine. Our results also show, however, that this use of quinidine may cause death, and on the basis of one of the probable mechanisms by which this comes about, they indicate, further, that the treatment with quinidine of ventricular tachycardia, from whatever cause, in the presence of an A-V block may be dangerous, because in this condition the abolition of the abnormal rhythm may be followed by a state of the ventricle that is much more serious, namely, complete ventricular arrest.

We cannot venture an explanation, at this time, of the reaction of the auricle to quinidine during the action of digitalis. We have assumed that the rapid auricular rhythm resulting from digitalis poisoning is a simple tachycardia of sinus origin. It is a rather striking fact that total doses of quinidine alone up to 40 mg cause only auricular acceleration, whereas doses as small as 3 mg during digitalis poisoning may cause auricular standstill. The mechanism involved requires further investigation.

#### SUMMARY AND CONCLUSIONS

1 Sixteen experiments were carried out to study the effects of quinidine in varying doses given intravenously (intramuscularly in one experiment) on the ventricular ectopic rhythms induced by digitalis in eleven normal unanesthetized dogs.

2 Although quinidine, even in very large doses, produces no change in the cardiac rhythm other than sinus acceleration in the normal dog, in the one in which digitalis has produced a ventricular tachycardia quinidine may accelerate or slow the heart rate, change the rhythm from one that is regular to one that is very irregular, or vice versa, and induce tetanic convulsions.

3 The aforementioned effects are due to one or more of the following changes in the cardiac mechanism: slowing of the ventricular tachycardia, abolition of the ventricular tachycardia, auricular or ventricular or complete cardiac standstill, establishment of a nodal rhythm or slow idioventricular rhythm or reestablishment of a normal sinus rhythm.

4 Changes in the regularity or irregularity of the rhythm are no guide as to whether a desirable or an undesirable change in the cardiac mechanism has occurred, as revealed in the electrocardiogram

5 Doses of quinidine that are harmless to the normal unanesthetized dog may produce death as the result of ventricular standstill in the dog in which digitalis has induced a ventricular tachycardia

6 The auricle (or sinus) also becomes very sensitive to depression by quinidine during the action of digitalis, so that doses which produce only acceleration of the auricle in the normal dog may produce auricular standstill during the auricular tachycardia resulting from digitalis poisoning

7 The foregoing effects may be produced by very small doses of quinidine, comparable to those used intravenously in man, namely, the equivalent of about from 2 to 6 grains (0.13 to 0.39 Gm.) for man

8 These effects of quinidine usually come on within less than a minute after the intravenous injection and are of very short duration, lasting only a few minutes in most cases. In a few instances some of them have been prolonged for considerable periods, with occasional interruptions, by repeated injections

9 The effects of quinidine vary not only with the dose of this drug but with the intensity of the digitalis poisoning. If digitalis has caused ventricular tachycardia without A-V block, quinidine will usually reestablish a normal rhythm (sinus [?] tachycardia). If digitalis causes an A-V block in addition, quinidine may now produce ventricular standstill after the ventricular tachycardia has been abolished

10 If small doses of quinidine fail to induce a normal sinus rhythm, large doses also fail to do so because under these conditions A-V block is usually present (masked by the ventricular tachycardia), and the effect of the quinidine, after slowing of the ventricle, is ventricular standstill

11 Ventricular standstill, sometimes for periods up to a minute or longer, as the result of relatively small doses of quinidine is common in the dog in which digitalis has produced a ventricular tachycardia

12 While in the normal dog large doses of quinidine induce clonic convulsions, two types of convulsions occur after quinidine in the overdigitalized dog, those appearing after small doses being tonic in character and due to prolonged periods of ventricular standstill

13 Double vagotomy does not appreciably alter any of these phenomena

14 While quinidine may produce a temporary desirable antagonistic effect in the case of ventricular tachycardia resulting from digitalis

poisoning, the difficulty of obtaining the necessary combination of actions and the possibility of producing ventricular standstill render its use dangerous for this purpose.

15 The probable mechanism of the ventricular standstill after quinidine during digitalis poisoning is described.

16 It is indicated that the use of quinidine to abolish ventricular tachycardia from any cause is dangerous in the presence of A-V block.

## Book Reviews

**Entstehung, Erkennung und Behandlung innerer Krankheiten** By Ludolf Krehl Volume 2 Second edition Price, 12 80 marks Pp 192 Berlin Julius Springer, 1932

This is the second of a three volume work on the pathogenesis, diagnosis and treatment of the diseases of internal medicine. The first volume of the trilogy was recently reviewed in the ARCHIVES, the last volume is still to come. The author, Dr Ludolf Krehl, for twenty-six years professor and head of the Medical Clinic of Heidelberg, is one of the great figures in German medicine. The present volume deals with diagnosis, it is excellent reading for the initiated, but cannot be recommended as a textbook, in fact, it cannot be intended for the beginner. Rather is it a charming essay, a fireside chatting, what a practitioner might expect to hear were he to enjoy an intimate visit with the master clinician, a confiding of the secrets of the trade and an exposition of those methods of procedure found effective.

The table of contents suggests a more systematic treatment of the subject than actually exists. The introductory sections deal with the art of diagnosis and clinical decision. The literature of the last twenty years is filled with contention as to whether medical procedure is science or art. Krehl is content to be a physician. Although the practice of medicine is largely built on scientific thought and method, the physician must go further than science is able to follow. Hesitation and doubt are necessary attributes of the scientist, but the physician must know his mind and act with resolution, intuition is required, an understanding of social difficulties and emotional conflicts, tact is indispensable, with an abundant sympathy. Krehl deplores the socialistic direction of modern medicine, especially in the German "Krankenkasse," whereby the relationship of patients to physicians becomes that of delinquents to a judge.

An intimate investigation of the psychic should be a part of every examination, a "psychoanalysis," not in the sense of the cult, but according to the true meaning of the word, and only when necessary. The vogue for indecent inquiry into the deeper processes of the soul is deplored as being frequently unnecessary and commonly harmful, it must do injury to sensitively organized persons. Everything here depends on the tact and insight of the physician who should do that which is required for elucidating the difficulties encountered, but nothing more.

The subsequent chapters are devoted to a critical discussion of the methods of examination and to the differential diagnosis of fever, the infectious diseases, the blood, the circulation, the respiration, the digestion, diseases of the kidneys and urinary tract, the nervous system, the muscles and the bone. Each topic is considered without an attempt at exhaustive or systematic treatment, but discursively and intimately as in informal conversation. The reader will feel amply repaid for the time he spends with these pages.

[EDITOR'S NOTE A review of volume 1 of this trilogy was published in the September, 1932, issue of the ARCHIVES, p 507. The title of this volume is "Pathologische Physiologie"]

**Clinical Endocrinology of the Female** By Charles Mazer, M D, Assistant Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania, Gynecologist to Mount Sinai and Northern Liberties Hospitals, Philadelphia, and Leopold Goldstein, M D, Demonstrator of Obstetrics, Jefferson Medical College, Assistant Gynecologist to Mount Sinai Hospital, Formerly Fellow in Gynecologic Research, University of Pennsylvania. Cloth Price, \$6 net Pp 518, with 117 illustrations Philadelphia W B Saunders Company, 1932

One of the most striking developments of recent medicine is the revolution that has taken place in ideas on gonadal function in relation to hormonal control



While the idea has gradually developed that such processes as menstruation, pregnancy and parturition, as well as aberrations from the normal course of these processes, are influenced by hormonal activity, the subject has been for the most part shrouded in mystery and has been confused by obviously futile and irrational "endocrine" therapy. Only in recent years has some suggestion of reason begun to flow from orderly and purposeful animal experimentation in this domain. As a matter of fact, so violent now is the torrent of publications and so bitter are the disagreements among able workers that one hardly dares hope that order can as yet emerge out of chaos.

In this well written, soundly tempered monograph one is tempted to say that the writers have achieved the impossible. Much of the material will doubtless require eventual revision—the subject is in too much of a state of flux for definitive treatment—but the statements are conservative and, above all, are documented by a scholarly and well selected bibliography. There is in brief, a summary of the fundamental physiology of the endocrine glands in relation to gynecology, as the matter stands today, with well reasoned applications to the various clinical disorders of the female genital processes. The reviewer feels that the book is unique in its field and is a storehouse of invaluable information for the physician who faces these distressing and perplexing problems.

**Herz- und Kreislaufinsuffizienz. Ein kurzes System der Störungen im Kreislaufsapparat.** By Dr K F Wenckebach. Band III. Price, 8 marks. Pp 120. Dresden. Theodor Steinkopff, 1931.

This "Buchlein" is one of a series of monographs designed primarily for the "praktischen Arzt," although, as Wenckebach adds, it may be of value to "Studierende" and to the "Kreislaufforscher." It presents an excellent, critical summary of the modern physiologic, biochemical and clinical aspects of circulatory failure.

Under cardinal circulatory disturbances it discusses failure of the left side of the heart, obstructions in the pulmonary circuit and failure of the right side of the heart. It appraises the importance, in the reverse order of the circulation, of obstruction of the great veins, the small veins and capillaries and, finally, the arterial system.

The second portion of the monograph is given over to a discussion of certain secondary aids to the circulation—"Muskularbeit," respiration, the peripheral heart, etc.—a discussion of water balance, body metabolism and blood volume and a final chapter on digitalis therapy and dyspnea.

The reviewer found himself particularly interested in the discussion of oxygen disturbance, anoxemia, coronary obstruction, cardiac infarction, etc., although possibly not being entirely in agreement with Wenckebach's views on spasm of the coronary artery. Similarly, he finds himself in agreement with the statement of the frequency of coronary thrombosis and the infrequency of coronary embolism as causes of cardiac infarction, but looks in vain for emphasis on the findings of single or multiple calcified sclerotic plaques alone (without thrombosis) as the cause of complete coronary occlusion with subsequent myocardial infarction.

Wenckebach has written, characteristically, a fine, lucid review of the salient topics of circulatory failure. One can wholeheartedly and enthusiastically recommend this monograph to those interested in this field of disturbed cardiac physiology.

**Fractures.** By Maurice Sinclair, CMG, MB, BCh (Edinburgh). Edited by G Gordon Taylor, OBE, MA, FRCS. Price, 24 shillings. Pp 539, with 337 illustrations. London. Constable & Co, Ltd, 1931.

This is a textbook on fractures for the practitioner. It is prefaced by a plea for improvement in the treatment of fractures generally, based on better knowledge of the fundamentals of anatomic relationships and practical mechanics. "Ninety per cent of good anatomical results are followed by good functional results" is the continuous emphasis made in this book.

The book is divided into two almost equal parts, the first dealing with general considerations, such as the principles of treatment, the influence of age and disease, signs and symptoms of fractures, repair of fractures, roentgen appearances, massage and movements, the end-results, complications, such as deformities and ununited fractures, the selection of the type of treatment, open operations, bone grafts, amputations, artificial limbs and medicolegal questions. Of these, the chapters on open operations and bone grafts are especially well written and contain information that would be difficult to locate elsewhere, with so little effort.

The second half discusses the treatment of individual fractures. Special emphasis is given to the management of fractures of long bones, clearly showing, with illustrations, the use of splints and appliances for obtaining the desired positions for the best end-results. In this field, the reviewer knows of no better text anywhere, because of the simple and clear way with which the subject is dealt. The chapters on the treatment of pelvic and skull fractures, in comparison with the rest of the book, are incomplete.

The book is richly illustrated with 337 x-ray photographs, photographs and diagrams. While knowledge of anatomy and the application of this knowledge are emphasized as requisite to successful treatment of fractures, no great amount of space is devoted to anatomic considerations. It is a practical textbook on treatment and, as such, is one of the best.

**The Sputum Its Examination and Clinical Significance** By Randall Clifford, M.D. Price, \$4 Pp 167, with 21 illustrations in black and white and 7 colored plates New York The Macmillan Company, 1932

To the physician who is accustomed to order the sending of a specimen of sputum to the laboratory for examination as a routine procedure and does not get first hand knowledge of the appearances of these various types of disease exudates, the contents of this monograph will quickly prove to him that he has neglected a major portion of his part of the clinical examination. It has been repeatedly shown that the physical signs commonly depended on by the clinician to diagnose pulmonary disorders originate in the first few millimeters of depth from the surface and as practically all of the morbid processes dealt with are exudative, it is readily apparent that much pertinent information may be obtained from a close ocular examination of the sputum. The trend of the modern physician to relegate this examination to the laboratory is a step backward. Probably the most accurate knowledge of the degree of severity of an inflammatory process is expressed in the quantity of purulent material produced. Very few modern hospital charts show such information.

To those laboratory workers who are content merely to report sputum as "negative" or "positive" for tubercle bacilli, a close study of the subject matter presented will reveal many sins of omission that may have meant life or death for many a patient. How often does one see elastic tissue reported? Yet the prompt recognition of this sign of degeneration of pulmonary tissue is of the utmost importance.

The text is well written, the interpretations of the findings are well supported by references, and the colored plates are particularly well executed.

**Fraktionierte Lumbalpunktion bei otogenen Meningitiden** By Aage Westergaard, Copenhagen Pp 213 Copenhagen Nyt Nordisk Forlag, Arnold Busck, 1931

By fractional lumbar puncture is understood the removal of liquor cerebrospinalis in a number of separate portions. It is a diagnostic procedure which the author of this book has elaborated and discussed in the minutest detail from observations on seventy-three patients, covering a period of four years.

The method is simple enough. The patient is placed in the right lateral prone position on a table the head end of which is elevated 30 cm, the knees being drawn up in the usual manner.

The puncture is made with 12 mm and 15 mm (external diameter) needles, respectively, for children and adults. The interspaces utilized are not mentioned, but presumably are the third and fourth lumbar. The liquor is collected in six portions of from 2 to 3 cc or 3 to 4 cc and immediately stoppered. The cells are then stained in the diluted fluid with a solution containing methyl violet and glacial acetic acid in definite proportions, and the number determined with the Fuchs-Rosenthal counting chamber. The results of these counts are graphically expressed in terms of unit volumes of cerebrospinal fluid.

Claims made are that the method is of clinical value in determining the prognosis of a meningeal infection, a rising curve denoting a diffuse meningitis. On the other hand, a declining or horizontal curve indicates a circumscribed process or perhaps that a diffuse meningitis is subsiding and becoming circumscribed. In the event that definite symptoms persist after an operative procedure with a horizontal or declining cell curve in the liquor, an endocranial abscess should be suspected.

**Man and Medicine** *An Introduction to Medical Knowledge* By Dr Henry E. Segerist, Professor at the University of Leipzig. With an Introduction by Dr William H. Welch, Professor of the History of Medicine, The Johns Hopkins University. Translated by Margaret Galt Boise. Cloth Price, \$4. Pp 340. New York: W. W. Norton & Company, Inc., 1932.

This book is an outline of the history and the development of medicine. When the medical reader turns the final page, he cannot be sure whether the author has been binding laurel to the plow or gilding the lily.

Beginning with Vesalius, the development of medicine is traced faithfully to its present state of advancement. The book is beautifully written, the literary style is excellent, and the scientific accuracy of detail bears witness to the author's knowledge of the subject, and perhaps gives a clue to his Teutonic antecedents. But there is a certain lack of imagination, a lack of inspirational or emotional push that one expects to find in works of this sort. This is doubtless due to the author's insistence on accuracy. Scientific accuracy and inspirational appeal are often incompatible. A recitation of more or less well known facts, even when expressed in such excellent style, is likely to leave the medical reader cold.

For the lay reader who wishes an authoritative and accurate outline of the development of medicine, written in terms that may be easily understood, this work cannot be too highly recommended.

**Fungous Diseases** *A Clinico-Mycological Text* By Harry C. Jacobson. Price, \$5.50. Pp 317. Springfield, Ill: Charles C. Thomas, 1932.

The subject of mycotic infections is rather a terror to most physicians, perhaps because of the inaccessibility of usable information. The brief comments found in most textbooks are obviously inadequate, whereas the large compendia are unintelligible to the average physician, who usually becomes lost in a plexus of terminology and in the well known disputes about classification. Hence the reviewer approached the present work, designed especially for the clinician, with hope and enthusiasm, his hopes were to some extent realized so far as the subject is reduced to a simple and yet reasonably comprehensive level. The author has a sound idea, but unfortunately the writing is marred not only by frequent errors in grammar but by an obscure, redundant and at times unreadable style. The format of the book is attractive, the illustrations are abundant and well selected, and the bibliography is adequate. The sections on therapy could be improved by a more critical evaluation of various measures and by more detailed instructions as to drug dosage and procedure.

# Archives of Internal Medicine

VOLUME 50

DECEMBER, 1932

NUMBER 6

## DECREASED DEXTROSE TOLERANCE IN ACUTE INFECTIOUS DISEASES

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AND

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Transient glycosuria has been noted in various infectious diseases. Hibbard and Morrissey<sup>1</sup> found it in diphtheria. Cammidge<sup>2</sup> stated that it occurs in diphtheria, scarlet fever, typhoid fever, influenza, appendicitis, measles and infections with suppuration. Buhl<sup>3</sup> described its occurrence in Asiatic cholera. Castellani and Willemore<sup>4</sup> and Harrison<sup>5</sup> have found that it may be present in malaria. Cammidge<sup>6</sup> and Higginson<sup>7</sup> have designated as "sapraemic glycosuria" that accompanying carbuncle or gangrene. This glycosuria is accompanied by a hyperglycemia according to Hollinger.<sup>8</sup>

A lowered dextrose tolerance was demonstrated by Hamman and Hirschman<sup>9</sup> in lobar pneumonia and acute tonsillitis. Olmsted and Gay<sup>10</sup> found abnormal blood sugar curves in many conditions including those resulting from acute infectious toxins. Tisdall, Drake and

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From the John McCormick Institute for Infectious Diseases

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2 Cammidge, P J. Glycosuria and Allied Conditions, London, E Arnold, 1913

3 Buhl. Mitteilungen aus der Pfeuferschen Klinik, Epidemische Cholera Ztschr f rationelle Med 6 1, 1855

4 Castellani, A, and Willemore, J. Glycosuria of Malarial Origin, *Brit M J* 2 286, 1921

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7 Higginson, C G. Sapraemic Glycosuria, *Brit M J* 1 296, 1921

8 Hollinger, A. Ueber Hyperglycemie bei Fieber, *Deutsches Arch f klin Med* 92 217, 1907-1908

9 Hamman, L, and Hirschman, I I. Studies on Blood Sugar. I Alimentary Hyperglycemia and Glycosuria as a Test of Sugar Tolerance, *Arch Int Med* 20 761 (Nov) 1917

10 Olmsted, W H, and Gay, L P. Study of Blood Sugar Curves Following a Standardized Glucose Meal, *Arch Int Med* 29 384 (March) 1922

Brown<sup>11</sup> noted a derangement of the carbohydrate metabolism in infants with acute infectious diarrhea. In the study of various infectious diseases Labbé and Boulin<sup>12</sup> found an increase in the height of the fasting blood sugar as well as in the height and duration of the curve after the administration of dextrose. Hector<sup>13</sup> was able to demonstrate considerable disturbance in the carbohydrate metabolism with lowering of the fasting blood sugar during the toxic stage of severe diphtheria. The studies of Andresen and Schmidt<sup>14</sup> revealed an increased blood sugar content in various infectious diseases excepting measles, and generally there were higher values during the febrile or toxic stages, but diphtheria was not studied. From the study of patients with malignant diphtheria, Lereboullet and Pierrot<sup>15</sup> found a hypoglycemia in a high percentage during the period of intense intoxication. Evans, Riding and Glynn,<sup>16</sup> in a study of oral sepsis, presented evidence of a slight but definite lowering of carbohydrate tolerance, which was less in the patients with acute alveolar abscess and was improved by treatment. Likewise, in general sepsis Thomson<sup>17</sup> found a temporarily defective carbohydrate metabolism. In arthritis also a deficient metabolism of carbohydrate has been emphasized by Pemberton and Foster<sup>18</sup>.

These clinical studies have been supplemented and to some extent confirmed by animal experimentation. Rosenthal<sup>19</sup> found in experimental diphtheria intoxication in rabbits a severe disturbance of carbohydrate metabolism which ended finally in a rapid fall of blood sugar. Tisdall, Drake and Brown<sup>20</sup> demonstrated the production of a lowered carbohydrate tolerance in puppies by the subcutaneous injection of large

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11 Tisdall, F. F., Drake, T. G. H., and Brown, A. The Carbohydrate Metabolism of Infants with Diarrhea, Infections and Acute Intestinal Intoxication, *Am J Dis Child* **30** 837 (Dec) 1925

12 Labbe, M., and Boulin, R. Disorders of Dextrose Regulation During the Course of Infections, *Bull et mem Soc med d hop de Paris* **49** 135 (Oct 30) 1925

13 Hector, Francis J. Carbohydrate Metabolism in Diphtheria, *Lancet* **2** 642, 1926

14 Andresen, J., and Schmidt, S. The Blood Sugar Content in Infectious Diseases, *Klin Wchnschr* **6** 213, 1927

15 Lereboullet, P., and Pierrot, R. Glycemia in Diphtheria, *Arch de med d enf* **31** 148, 1928

16 Evans, W. H., Riding, H., and Glynn, E. E. The Influence of Oral Sepsis upon Carbohydrate Tolerance in Non-Diabetics, *Lancet* **2** 592, 1927

17 Thomson, D. B. Influence of Sepsis and Endocrine Disturbances on Carbohydrate Metabolism, *Glasgow M J* **112** 25, 1929

18 Pemberton, R., and Foster, G. L., quoted by Olmsted and Gay<sup>10</sup>

19 Rosenthal, F. Disturbance of Carbohydrate Metabolism in Experimental Diphtheria Intoxication, *Arch f exper Path u Pharmacol* **75** 99, 1914

20 Tisdall, F. F., Drake, T. G. H., and Brown, A. The Production of a Lowered Carbohydrate Tolerance in Dogs, *Am J Dis Child* **32** 854 (Dec) 1926

doses of diphtheria toxin Sweeney and Lackey<sup>21</sup> confirmed these observations on rabbits

By studying the pathologic changes in the organs of rabbits dying from an enteritidis—paratyphoid B infection, Menten and Manning<sup>22</sup> were able to demonstrate degenerative changes in the islets of Langerhans of the pancreas Later, by the injection of these same organisms into rabbits, these authors<sup>23</sup> found a marked increase in the concentration of the blood sugar Similar lesions were found by Thomas<sup>24</sup> in the pancreas of guinea-pigs dying of the same infection Zeckwer and Goodell<sup>25</sup> observed a rapid rise in the blood sugar level of rabbits following the intravenous injection of certain killed bacteria and with but little change in the blood sugar with other organisms Charrin and Carnot<sup>26</sup> produced glycosuria in three of twelve dogs by injecting bacteria into the pancreatic duct Barber<sup>27</sup> observed a hyperglycemia in experimental cholecystitis in dogs

#### DIABETES FOLLOWING ACUTE INFECTIONS

It is now generally recognized that there is a marked lessening of dextrose tolerance with infection in diabetes mellitus, and enormous doses of insulin are required to control an acidosis in a diabetic person whose usual endogenous supply would be sufficient under ordinary conditions Graham<sup>28</sup> has emphasized the frequency with which bacterial infection is the cause of the onset of coma in diabetes mellitus Most authors give infection a small place as a factor in the etiology of diabetes Joslin<sup>29</sup> could find a history of an antecedent infection in about 15 per cent of his cases Peters<sup>30</sup> has reported some cases in

21 Sweeney, J S, and Lackey, R W The Effect of Toxemia on Tolerance for Dextrose, *Arch Int Med* **41** 257 (Feb) 1928

22 Menten, M L, and Manning, H M Pathological Changes in Organs of Rabbits Dying Spontaneously from Enteritidis-Paratyphoid B Infections, *J M Research* **44** 674, 1923-1924

23 Menten, M L, and Manning, H M Blood Sugar Studies on Rabbits Infected with Organisms of the Enteritidis-Paratyphoid B Group, *J M Research* **44** 675, 1923-1924

24 Thomas, B G H Occurrence of Organisms of the Enteritidis Paratyphoid B Group in Guinea-Pigs, *J Infect Dis* **35** 407 (Nov) 1924

25 Zeckwer, I T, and Goodell, H Blood Sugar Studies I Rapid Alterations in the Blood Sugar Level of Rabbits as Result of Intravenous Injections of Killed Bacteria of Various Types, *J Exper Med* **42** 43, 1925

26 Charrin and Carnot Diabetes and Microbes, *M Week* **2** 259 and 532, 1894

27 Barber, W H Hyperglycemia Following Experimental Cholecystitis, *Proc Soc Exper Biol & Med* **23** 101, 1925

28 Graham, G The Relation of Infection to Diabetic Coma, *Quart J Med* **18** 294, 1925

29 Joslin, E P Treatment of Diabetes Mellitus, ed 4, Philadelphia, Lea & Febiger, 1928

30 Peters, J P The Effect of Infection on Diabetes and Glycosuria, *Proc Connecticut M Soc*, 1923, p 190

which the diabetes was preceded<sup>31</sup> by an acute infection Geyelin<sup>31</sup> stated that he had seen eight cases in which the diabetes arose within five weeks after an acute infection White<sup>32</sup> in the study of one hundred diabetic children found that only 2 per cent did not have a history of acute infections preceding the onset of the diabetes It seems to be well accepted that diabetes, even in a fulminating form, can follow acute infectious diseases such as typhoid fever, scarlet fever, cholera, influenza, diphtheria, enteric fever, tonsillitis, malaria, syphilis and rheumatic fever Patrick<sup>33</sup> reported a case of acute diabetes which followed an attack of mumps, and Gunderson<sup>34</sup> believes that epidemics of mumps are followed by a rise in the death rate from grave diabetes in the young within the three or four years following each successive epidemic Holcomb<sup>35</sup> reported two cases of diabetes in which the onset was accompanied or preceded by focal infection Beck and Pollock<sup>36</sup> have observed that pathologic conditions of the ear, nose and throat are not infrequently found in diabetes In a statistical study of diabetes as compared with other general diseases, Barach<sup>37</sup> found that diabetes was more commonly preceded by chronic tonsillitis, typhoid fever and pneumonia than were other chronic diseases

It is well known that diabetes mellitus may follow closely or accompany acute pancreatitis Recently such cases have been reported by Dunn, Vatcher and Woodward,<sup>38</sup> by Foord and Bowen<sup>39</sup> and by Warfield<sup>40</sup> Adams<sup>41</sup> thinks that disease of the gallbladder is a doubtful factor in the etiology of diabetes mellitus, but Lichty and Woods<sup>42</sup> expressed the opinion that diseases of the gallbladder and bile ducts

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31 Geyelin, H R, in Cecil, R L Text Book of Medicine, ed 2, Philadelphia, W B Saunders Company, 1930

32 White, P The Potential Diabetic Child, *J A M A* **88** 170 (Jan 15) 1927

33 Patrick, A Acute Diabetes Following Mumps, *Brit M J* **2** 802, 1924

34 Gunderson, E Is Diabetes of Infectious Origin? *J Infect Dis* **41** 197 (Sept) 1927

35 Holcomb, B The Influence of Focal Infections in Diabetes as Shown by Alterations of the Blood Sugar Curve, *J Lab & Clin Med* **11** 874, 1926

36 Beck, J C, and Pollock, H L Pathologic Conditions of the Ear, Nose and Throat in Diabetes, *Arch Otolaryng* **5** 400 (May) 1927

37 Barach, J H Etiologic Factors in Diabetes, *Arch Int Med* **39** 636 (May) 1927

38 Dunn, J P S Vatcher, S, and Woodward, A S Diabetes as Sequela to Acute Pancreatitis *Lancet* **1** 595, 1926

39 Foord, Alvin G, and Bowen, Byron D Acute Interstitial Pancreatitis in Two Cases of Diabetic Coma, *Am J M Sc* **180** 676, 1930

40 Warfield, L M Acute Pancreatitis Followed by Diabetes, *J A M A* **89** 654 (Aug 27) 1927

41 Adams, S F Is Disease of the Gall Bladder a Cause of Diabetes Mellitus? *Surg, Gynec & Obst* **41** 75, 1925

42 Lichty, J A, and Woods, J O The Significance of Glycosuria in Gall Bladder and Duct Diseases *Am J M Sc* **167** 1, 1924

may be later complicated by diabetes. They cited three patients who recovered from diabetes mellitus and disease of the gallbladder after operation. Rabinowitch<sup>43</sup> in a statistical study found "nine times as many patients with gall bladder disease had diabetes as had the patients in general." Stansfield and Warren<sup>44</sup> have reported two autopsies on diabetic children in which there was lymphocytic infiltration of the islets of Langerhans. Such changes together with the history suggested that the diabetes was of infectious origin.

An explanation for the loss of tolerance in acute infections may be found in the effect of toxemias on the action of insulin. Lawrence and Buckley<sup>45</sup> noted an inhibition of insulin action by diphtheria toxin in rabbits, and sought an explanation in the overactivity of the thyroid-adrenal apparatus. Sweeney<sup>46</sup> observed that injected insulin produced essentially the same effect on the blood sugar of rabbits in the presence of a gradually rising toxemia from diphtheria toxin, and hence concluded that the "effect of toxemia is that of a suppression of endogenous production of insulin." Schwentker and Noel<sup>47</sup> studied the carbohydrate metabolism in children with diphtheria and in rabbits with diphtheria intoxication, and concluded that there is primarily an increased glycogenolysis followed by a decreased glycogenesis, which they ascribed to a suppression of the endogenous production of insulin. They also found that the administration of insulin caused an assimilation of dextrose in such cases.

#### THE SCOPE OF THE PRESENT WORK

The present work includes 1. The study of acute infectious diseases in patients by means of dextrose tolerance tests in which 100 Gm of dextrose in lemonade was given to adults and approximately 1 Gm per pound to children. The dextrose was given before breakfast or after fasting, and all these patients were given the usual hospital diet for such diseases. The urine was saved in six hour specimens for twenty-four hours, and the amount of sugar was determined quantitatively by the Folin-

43 Rabinowitch, I. M. The Incidence of Diabetes Mellitus in Diseases of the Gall Bladder and Its Passages, *Canad. M. A. J.* **14** 296, 1924.

44 Stansfield, O. H., and Warren, S. Inflammation Involving the Islands of Langerhans in Diabetes, *New England J. Med.* **198** 686, 1928.

45 Lawrence, R. D., and Buckley, M. B. The Inhibition of Insulin Action by Toxemias and Its Explanation. I. The Effect of Diphtheria Toxin on Blood Sugar and Insulin Action in Rabbits, *Brit. J. Exper. Path.* **8**:58, 1927.

46 Sweeney, J. S. Effect of Toxemia on Tolerance for Dextrose and on the Action of Insulin, *Arch. Int. Med.* **41** 420 (March) 1928.

47 Schwentker, F. F., and Noel, W. W. The Circulatory Failure of Diphtheria. II. The Carbohydrate Metabolism in Diphtheria Intoxication, *Bull. Johns Hopkins Hosp.* **46** 259, 1930.



Berglund<sup>48</sup> method 2 The determination of the blood sugar of such patients during fasting by the Folin-Wu method 3 The effect of the administration of dextrose and insulin on acute infections 4 The production of experimental acute infections in animals and a study of the dextrose tolerance by means of quantitative dextrose determinations on the daily twenty-four hour specimens of urine and by repeated blood sugar curves

#### ACUTE INFECTIOUS DISEASES

In table 1 are summarized the results of the study of one hundred and eight patients, including sixty-seven patients with scarlet fever, seventeen with diphtheria, eight with pneumonia, five with influenza, three with acute tonsillitis, three with measles and one each with erysipelas, encephalitis, mumps, epidemic meningitis and poliomyelitis. Ten normal subjects are also included.

TABLE 1—*Dextrose Tolerance Test in Acute Infectious Diseases, Febrile Stage*

Disease	Number of Patients	Dextrose, Gm. Excreted in 6 Hour Specimen			Dextrose, Gm. Excreted in 24 Hour Specimen		
		Maximum	Minimum	Average	Maximum	Minimum	Average
Scarlet fever	67	4.41	0.10	0.75	5.51	0.23	1.05
Diphtheria	17	3.08	0.19	0.82	4.46	0.42	1.21
Pneumonia	8	2.30	0.15	0.87	3.50	0.24	1.66
Influenza	5	5.01	0.21	1.26	5.70	0.51	1.71
Miscellaneous*	11	6.94	0.14	1.28	7.31	0.29	1.61
Normal	10	0.18	0.04	0.11	0.42	0.13	0.31

\* Acute tonsillitis, measles, erysipelas, encephalitis, mumps, epidemic meningitis and poliomyelitis.

The patients with scarlet fever ranged from 2 to 33 years of age. The total amount of dextrose excreted in the urine during the six hour period immediately following the ingestion of dextrose varied from 0.1 to 4.41 Gm., averaging 0.75 Gm. for each patient. In eleven of these patients the amount exceeded 1 Gm. The total amount of dextrose excreted in the twenty-four hours (including the first six hours) immediately following the tolerance test varied from 0.23 to 5.51 Gm. and averaged 1.05 Gm. In thirteen patients the amount for the twenty-four period exceeded 1 Gm., and in twenty-four the values fell within the limits of the normal group. Twenty-four patients each had a sufficient quantity of dextrose in the urine to give a positive Hanes test.

Thirty-nine of the sixty-seven patients with scarlet fever were studied again after an interval of from ten to fourteen days following the initial study. The figures for the six hour period varied from 0.02 to 1.6 Gm., averaging 0.15 Gm., and for the twenty-four hour period they were from 0.09 to 1.76 Gm., averaging 0.32 Gm. The results are seen

<sup>48</sup> Folin, O., and Berglund, H. A Colorimetric Method for the Determination of Sugars in Normal Human Urine, *J. Biol. Chem.* **51**: 209, 1922.

in table 2 This same group was studied again from twenty-one to twenty-eight days after the onset of the disease (table 3), in the six hour period the amount of dextrose excreted ranged from 0.02 to 0.27 Gm, averaging 0.08 Gm, whereas the values for the twenty-four hour period ranged from 0.07 to 0.54 Gm, averaging 0.28 Gm

There were seventeen patients with diphtheria whose ages varied from 4 to 42 years The total amount of dextrose excreted in the six hour period varied from 0.19 to 3.08 Gm and averaged 0.82 Gm, in the twenty-four hour period these values ranged from 0.42 to 4.46 Gm and averaged 1.21 Gm The tolerance tests were repeated shortly after the subsidence of symptoms For the six hour period the figures varied from 0.06 to 0.13 Gm, averaging 0.11 Gm, for the twenty-four hour

TABLE 2—*Dextrose Tolerance Test in Acute Infectious Diseases from Ten to Fourteen Days After Admission*

Disease	Number of Patients	Dextrose, Gm Excreted in 6 Hour Specimen			Dextrose, Gm Excreted in 24 Hour Specimen		
		Maximum	Minimum	Average	Maximum	Minimum	Average
Scarlet fever	39	1.60	0.02	0.15	1.76	0.09	0.32
Diphtheria	9	0.13	0.06	0.11	0.53	0.16	0.31
Pneumonia	3	0.92	0.10	0.40	2.00	0.21	0.83

TABLE 3—*Dextrose Tolerance Test in Acute Infectious Diseases from Twenty-One to Twenty-Eight Days After Admission*

Disease	Number of Patients	Dextrose, Gm Excreted in 6 Hour Specimen			Dextrose, Gm Excreted in 24 Hour Specimen		
		Maximum	Minimum	Average	Maximum	Minimum	Average
Scarlet fever	36	0.27	0.02	0.08	0.54	0.07	0.28
Diphtheria	2	0.12	0.06	0.09	0.35	0.15	0.25
Pneumonia	1			0.28			0.81

period, from 0.16 to 0.53 Gm, with an average of 0.31 Gm Of these patients with diphtheria, four had dextrose values in excess of 1 Gm for the six hour period, and in three the value was more than 2 Gm In three patients the amount fell within the normal range The urine of eight patients contained a sufficient quantity of dextrose to give a positive Haines test

The eight patients with pneumonia varied in age from 3 to 60 years The amount of dextrose in the urine varied from 0.15 to 2.3 Gm, averaging 0.87 Gm, for the six hour period, and from 0.24 to 3.50 Gm, averaging 1.66 Gm, for the twenty-four hour period Three of these patients were again tested after the crisis The amount of dextrose in the urine for the six hour period varied from 0.10 to 0.92 Gm, with 0.4 Gm as the average, for the twenty-four hour period these values were from 0.21 to 2 Gm, averaging 0.83 Gm In two patients the loss of tolerance persisted long after recovery from the

pneumonia, and it was found necessary to restrict the carbohydrate content of the diet for several weeks. In four cases the amount of dextrose excreted in six hours was in excess of 1 Gm, and in two (both mild cases of bronchopneumonia) the values were normal. Haines' test of the urine was positive in five patients.

Five patients with influenza were studied, and the loss of tolerance in two of these was quite evident. For the six hour period the amount of dextrose excreted ranged from 0.21 to 5.01 Gm, and averaged 1.26 Gm, the corresponding values for the twenty-four hour period were from 0.51 Gm to 5.70 Gm, averaging 1.71 Gm. In two of these the quantity of dextrose for the six hour period exceeded 1 Gm, and in two the values were normal. In three patients there was glycosuria.

There were eleven patients in the group classed as "miscellaneous," and the quantitative excretion of dextrose in the six hour specimen varied from 0.14 to 6.94 Gm, averaging 1.28 Gm, for the twenty-four hour period the figures were from 0.23 to 7.31 Gm, with an average of 1.61 Gm. The patient whose values were the highest had measles shortly after recovery from diphtheria. Another patient with measles excreted 1.01 Gm of dextrose in six hours and 1.51 Gm in twenty-four hours. Two patients with acute tonsillitis had dextrose values of 1.62 and 2.73 Gm for the six hour period and 2.04 and 3.01 Gm, respectively, for the twenty-four hour period. Thus in four of the eleven the amount of dextrose excreted in the six hour period exceeded 1 Gm. Six patients of this group had glycosuria, and in three the values were normal.

Ten subjects without fever and without clinical evidence of an altered carbohydrate metabolism were studied. The values for this group varied from 0.04 to 0.18 Gm of dextrose averaging 0.11 Gm in the six hour period, for the twenty-four hour period they ranged from 0.13 to 0.42 Gm, averaging 0.31 Gm. None of these subjects had glycosuria by Haines' test.

In summarizing the study of the patients with acute infections, it can be noted that the most marked decrease in tolerance usually occurred in those who were severely ill or who had one disease followed by complications or sequelae or in those in whom two or more contagious diseases developed in quick succession.

#### BLOOD SUGAR DURING FASTING

The blood sugar during fasting was estimated in twelve patients with various acute contagious diseases, and the concentration of dextrose varied from 0.097 to 0.145 Gm per hundred cubic centimeter, averaging 0.115 Gm. The two highest values were obtained in patients with pneumonia.

DEXTROSE TOLERANCE TESTS MADE WITH 0.5 GM OF DEXTROSE  
PER POUND OF WEIGHT

These tests were made on eighty-eight patients fifty-one with scarlet fever, thirty-two with diphtheria, three with measles and two with acute tonsillitis. In this group 50 Gm of dextrose was given to adults and 0.5 Gm per pound to children. It was found that the smaller amount of dextrose caused less discomfort in some patients and that the values, although slightly lower, gave a good indication of the patient's tolerance. The six hour period only was used for this group, and the results are summarized in table 4.

The values obtained for patients with scarlet fever were maximum, 3.85 Gm, minimum, 0.03 Gm, and average, 0.63 Gm. In nine patients the amount exceeded 1 Gm and in fourteen the quantity of dextrose was sufficient to give a positive Haines test.

Among the thirty-two patients with diphtheria the maximum amount of dextrose excreted by any one patient in six hours was 4.01 Gm, the

TABLE 4—*Dextrose Tolerance Test in Acute Infectious Diseases Without Insulin\**

Diseases	Number of Patients	Dextrose, Gm Excreted in 6 Hour Specimen Without Insulin		
		Maximum	Minimum	Average
Scarlet fever	51	3.85	0.03	0.63
Diphtheria	32	4.01	0.03	0.98
Measles	3	0.99	0.08	0.40
Tonsillitis	2	2.73	0.13	1.43
Normal	4	0.14	0.06	0.10

\* 0.5 Gm of dextrose given per pound

minimum, 0.03 Gm, and the average, 0.98 Gm. Eleven of these patients had an amount in excess of 1 Gm, fourteen gave a positive Haines test and eight had normal values.

The three patients with measles gave the following results for the six hour period: 0.08, 0.10 and 0.99 Gm. The figures for the two with acute tonsillitis were 0.13 and 2.73 Gm.

Four subjects whose carbohydrate metabolism was thought to be normal were studied, and the values for the dextrose excreted were 0.06, 0.08, 0.14 and 0.11 Gm.

#### THE EFFECT OF INSULIN

The effect of insulin on the carbohydrate tolerance and also on the course of the diseases, scarlet fever and diphtheria, was studied in twenty-nine patients. The results, both without and with insulin, are summarized in table 5.

Before insulin was given the amount of dextrose excreted in the urine for the six hours after the ingestion of dextrose was maximum,

6.51 Gm, minimum, 0.23 Gm, and average, 1.73 Gm. After from 10 to 15 units of insulin was injected, the corresponding values were 3.01, 0.04 and 0.69 Gm. Thus, on the average, more than 1 Gm of dextrose per patient was utilized on the addition of the insulin. Without insulin, fourteen of the patients had more than 1 Gm of dextrose in the urine, whereas only six of the same patients excreted more than 1 Gm of sugar following the injection of insulin. In three patients, however, in whom the course of the disease was fluctuating, the amount with insulin was greater than the amount without it.

An additional group of seventeen patients with diphtheria and scarlet fever was given insulin on the day of admission to the hospital and with the initial dextrose tolerance test. These results are also seen in table 5. The amount in the urine for the six hour period varied from 0.06 to 3.61 Gm, averaging 0.65 Gm, figures practically equivalent to those for the group given insulin with a second dextrose tolerance test.

TABLE 5—*Dextrose Tolerance Test in Acute Infectious Diseases Without and With Insulin (from Ten to Fifteen Units) \**

Diseases	Number of Patients	Dextrose, Gm Excreted in 6 Hour Specimen Without Insulin			Dextrose, Gm Excreted in 6 Hour Specimen With Insulin		
		Maximum	Minimum	Average	Maximum	Minimum	Average
Diphtheria and scarlet fever	29	6.51	0.23	1.73	3.01	0.04	0.69
Diphtheria and scarlet fever	17				3.61	0.06	0.65
Diphtheria and scarlet fever (repeated)	5	6.40	0.37	2.05	1.99	0.10	0.53

\* 0.5 Gm of dextrose given per pound

Five patients were studied repeatedly by means of the dextrose tolerance test, with and without insulin, and the average amount of dextrose in the urine for six hours was, respectively, 0.53 and 2.05 Gm. By increasing the dose of insulin from 10 to 15 units the average amount of dextrose in the urine was reduced slightly.

Sixteen patients were given from 10 to 35 Gm of dextrose in addition to the regular diet two or three times daily, and from 5 to 15 units of insulin was injected about twenty minutes preceding the ingestion of dextrose. The clinical course of these patients was followed carefully, and although all these patients made a satisfactory recovery it could not be demonstrated conclusively that their improvement was more rapid than that of similar patients not given additional dextrose and insulin.

#### EXPERIMENTAL INFECTIONS IN ANIMALS

The tolerance of twenty-nine normal rabbits was ascertained by injecting intravenously at intervals of from three to ten days sufficient 10 per cent solution of dextrose to give a positive Haines test in the

urine The tolerance was found to vary only slightly in different normal animals and to average 1.0 Gm per kilogram.

Experimental infections were then produced in twenty-one rabbits by injecting a forty-eight hour broth culture of the organisms into the

TABLE 6—*Excretion of Dextrose in Experimental Infections in Rabbits and Dogs*

	Broth Culture of Organisms, Cc	Normal, Gm	Maximum Dextrose Excreted, Gm	Minimum Dextrose Excreted, Gm	Average Dextrose Excreted, Gm	Animal	Comment
Scarlet fever streptococcus	4.5	0.030	0.104	0.026	0.039	Rabbit 1	Died after 25 days
Scarlet fever streptococcus	0.525	0.036	0.116	0.021	0.060	Rabbit 2	Died after 14 months
Scarlet fever streptococcus	1.55	0.036	0.116	0.011	0.058	Rabbit 3	Died after 13 months
Pneumococcus type I	0.535	0.022	0.117	0.023	0.039	Rabbit 4	Died after 6 months
Pneumococcus type I	0.540	0.027	0.296	0.027	0.073	Rabbit 5	Died after 5½ months
Typhoid bacillus	0.512	0.035	0.126	0.021	0.076	Rabbit 6	Died after 6 months
Typhoid bacillus	1.10	0.040	0.073	0.021	0.044	Rabbit 7	Died after 1 month
Typhoid bacillus	0.55	0.034	0.112	0.015	0.052	Rabbit 14	Died after 5½ months
Erysipelas streptococcus	5.35	0.030	0.160	0.027	0.091	Rabbit 8	Died after 3 months
Erysipelas streptococcus	2.30	0.030	0.096	0.013	0.040	Rabbit 17	Died after 6 months
Influenza bacillus	10.50	0.043	0.091	0.029	0.039	Rabbit 9	Died after 4½ months
Influenza bacillus	1.6	0.030	0.055	0.035	0.043	Rabbit 15	Died after 3 months
Pneumococcus type III	1.10	0.043	0.169	0.033	0.069	Rabbit 10	Died after 7 weeks
Pneumococcus type III	1.10	0.030	0.125	0.041	0.073	Rabbit 12	Died after 6 weeks
Pneumococcus type III	1.65	0.013	0.076	0.006	0.023	Rabbit 13	Living after 1 year
Scarlet fever anaerobic organisms	0.51	0.022	0.044	0.039	0.042	Rabbit 19	Died after 3 weeks
Scarlet fever anaerobic organisms	0.425	0.026	0.085	0.025	0.050	Rabbit 20	Living after 5 months
Scarlet fever anaerobic organisms	0.210	0.035	0.062	0.032	0.050	Rabbit 21	Died after 1 month
Scarlet fever anaerobic organisms	0.225	0.026	0.037	0.017	0.028	Rabbit 24	Living after 4 months
Scarlet fever anaerobic organisms	0.312	0.023	0.082	0.010	0.040	Rabbit 25	Died after 7 weeks
Paratyphoid B bacillus	0.206	0.018	0.106	0.034	0.054	Rabbit 26	Died after 1 month
Average		0.030	0.108	0.024	0.054		
Normal values (3 tests)		0.030	0.030	0.010	0.030	29	
Broth injected (5 tests)		0.027	0.053	0.013	0.027	2	
Salt injected (5 tests)		0.030	0.049	0.020	0.030	2	
Typhoid bacillus	0.75	0.067	0.169	0.012	0.077	Dog 2	Died after 17 days
Typhoid bacillus	0.575	0.060	0.384	0.040	0.138	Dog 3	Living after 9 months

veins of the ear daily in an increasing amount for several days, thence at intervals of two or three days for a few weeks and finally, when a satisfactory dose was established, at weekly intervals for several months. The urine was collected daily and the amount of dextrose

determined quantitatively by means of the Folin-Berglund<sup>48</sup> method, modified by first rendering the urine acid with dilute sulphuric acid. The results of this study can be seen in table 6. The figures recorded are averages for the three days preceding the first injection (normal period) and for two or three days immediately following it.

Scarlet fever streptococci were used in three rabbits, a forty-eight hour broth culture being injected intravenously in amounts varying from 0.5 to 55 cc. In one of these rabbits a subcutaneous abscess was produced by injecting the organisms mixed with sterilized kaolin. A trace of sugar was repeatedly detected by Haines' qualitative test. One rabbit died after twenty-five days, but the other two lived for fourteen and

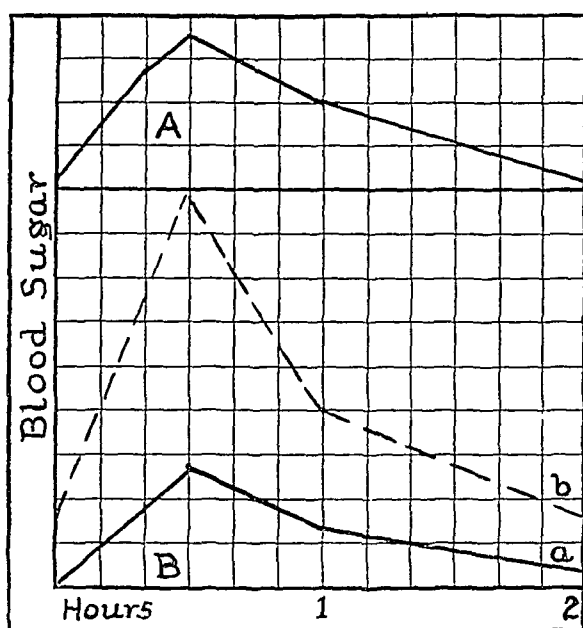


Chart 1—*A*, blood sugar curve of rabbit 2 on July 25, 1931, one month after an injection of scarlet fever streptococci. Each division on the vertical scale at the left indicates 0.02 per cent. *B*, blood sugar curves of rabbit 3: *a*, curve obtained Dec. 23, 1930, twenty-four hours after an injection of scarlet fever streptococci; *b*, curve obtained on Feb. 23, 1931, twenty-four hours after an injection of scarlet fever streptococci; *c*, curve obtained on July 23, 1931, one month after an injection of scarlet fever streptococci. The divisions on the vertical scale at the left indicate tenths per cent.

thirteen months respectively. The average amount of dextrose excreted was 0.059 Gm. or practically double the average normal value, 0.030 Gm. Repeated dextrose tolerance tests revealed considerable reduction in tolerance. Blood sugar curves are shown for rabbits 2 and 3 (chart 1).

Pneumococcus type I was injected into two rabbits in amounts varying from 0.5 to 40 cc., and sugar appeared in the urine of rabbit 5, the

total amount excreted for one twenty-four hour period being 0.296 Gm. The average amount excreted was 0.066 Gm daily, or more than twice the normal daily average of 0.024 Gm. Dextrose tolerance tests revealed at times as much as a 50 per cent reduction in tolerance. The blood sugar curve for rabbit 4 is shown. One rabbit lived for six months and the other for five and a half months.

The typhoid bacillus was used for experiments on three rabbits, and amounts of culture varying from 0.5 to 12 cc. were injected. Dextrose

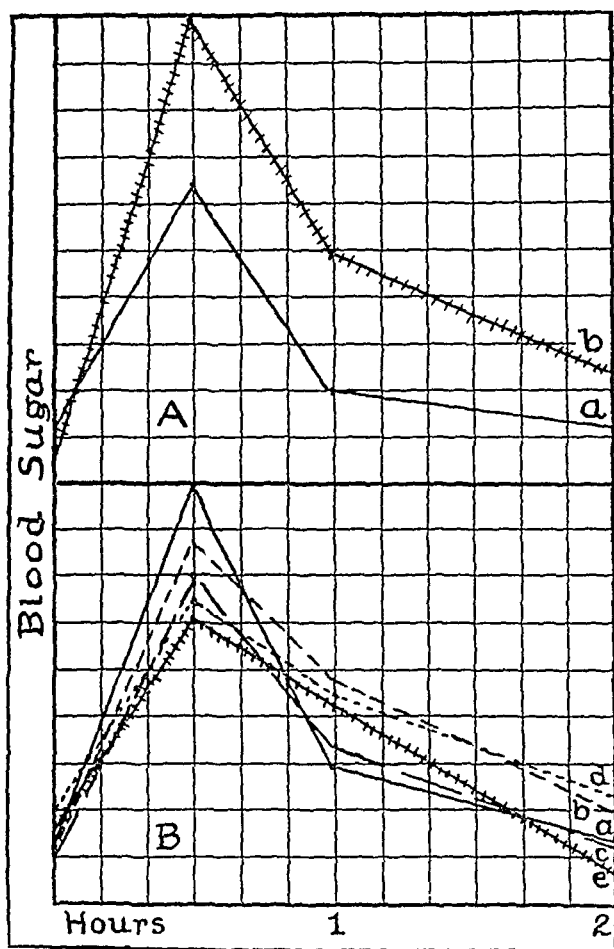


Chart 2—A, blood sugar curves of rabbit 6 *a*, curve obtained four days after infection with typhoid (Jan 3, 1931), *b*, curve obtained one week after injection of typhoid bacilli (Feb 16, 1931) when the animal was weak and dying. In this and subsequent charts each division on the vertical scale at the left indicates 0.02 per cent. B blood sugar curves of rabbit 14 *a*, curve obtained before typhoid, *b*, curve obtained two days after the injection of typhoid organisms (April 5, 1931), *c*, curve obtained one week after the injection of typhoid organisms (May 4, 1931), *d*, curve obtained three days after infection with typhoid (May 27, 1931), *e* curve obtained three weeks after infection (July 13, 1931).

appeared in the urine in quantities sufficient to give a positive Hames test on several occasions with rabbits 6 and 14 and in traces with rabbit 7. Tolerance tests with injected dextrose disclosed a 30 to 50 per cent



reduction in tolerance temporarily. The average daily amount of dextrose excreted in the urine during the forty-eight hours following the experimental infection was 0.064 Gm. Blood sugar curves are exhibited for rabbits 6 and 14 in chart 2.

Two rabbits were given erysipelas streptococcus culture in quantities varying from 2 to 35 cc. A subcutaneous abscess was produced in rabbit 8. A trace of dextrose was detected by the Haines test in the urine of both rabbits, and the maximum amount determined quantitatively was 0.160 Gm. in twenty-four hours. The average daily excretion was 0.065 Gm. Rabbit 8 lived for three months and rabbit 17 for six

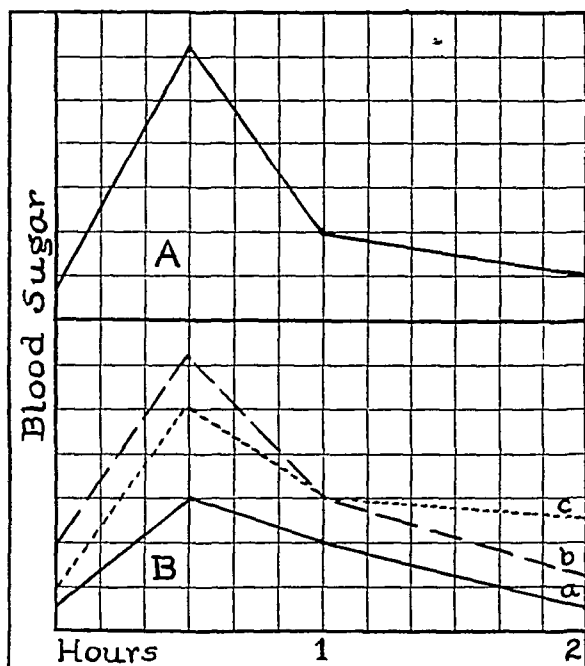


Chart 3—A, blood sugar curve of rabbit 8, thirty-three days after the injection of erysipelas streptococci. B, blood sugar curves of rabbit 17: a, curve before injection of erysipelas organisms (April 9, 1931), b, curve obtained twenty-four hours after the injection of erysipelas streptococci (May 4, 1931).

months. Dextrose tolerance tests revealed about a 25 per cent reduction in tolerance to injected dextrose. Blood sugar curves (chart 3) indicated a slight reduction in tolerance.

Rabbits 9 and 15 were given cultures of influenza bacilli in volumes varying from 1 to 50 cc. An abscess beneath the skin of the back was produced in rabbit 9. Only traces of dextrose were found in the urine, and the average daily excretion was 0.51 Gm. These rabbits lived four and one-half and three months, respectively. Intravenous tolerance tests revealed about a 30 per cent reduction at one time in rabbit 9 but normal values later.

Pneumococcus type III was used with rabbits 10, 12 and 13 in quantities varying from 1 to 10 cc. Dextrose appeared in the urine on one occasion with rabbit 10 and in traces at several times with all three rabbits, and the maximum amount excreted in twenty-four hours by rabbits 10 and 12 was 0.169 and 0.125 Gm, respectively, the average daily excretion of these two rabbits was 0.071 Gm. They lived seven and six weeks. Rabbit 13 was particularly resistant to pneumococci and was less affected than any other of the twenty-one rabbits. The average amount of dextrose excreted per day was only 0.023 Gm as compared

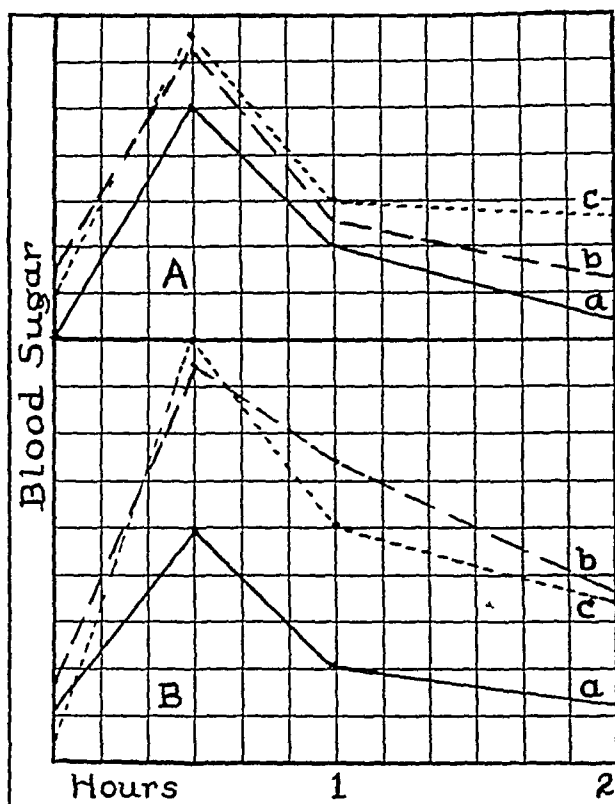


Chart 4—A, blood sugar curves of rabbit 10 a, curve obtained before an injection of pneumococci, type III (Jan 14, 1931), b, curve obtained twenty-four hours after an injection of these organisms (Feb 7, 1931), c, curve obtained twenty-four hours after an injection (Feb 23, 1931) B, blood sugar curves of rabbit 13 a, curve obtained before an injection of pneumococci, type III (Feb 3, 1931), b, curve obtained twenty-four hours after an injection of pneumococci, type III (April 23, 1931), c, curve obtained forty-eight hours after an injection of pneumococci (June 3, 1931)

with the normal 0.013 Gm. The animal is still living after one year. Dextrose tolerance tests indicated slight reduction of tolerance at first, but increased tolerance later. The blood sugar curves for rabbits 10 and 13 are plotted in chart 4.

An anaerobic broth culture was made from the throats of patients with scarlet fever, and quantities of this suspension varying from 0.2 to

2.5 cc were used to inoculate five rabbits. Three rabbits died after three, four and seven weeks, respectively, and two are living after five and four months. The average amount of dextrose excreted varied from 0.028 to 0.050 Gm, and averaged 0.042 Gm, as contrasted with 0.026 Gm, the average for the normal period. Tests revealed a slight impairment of dextrose tolerance. The blood sugar curves of rabbit 20 are plotted in chart 5.

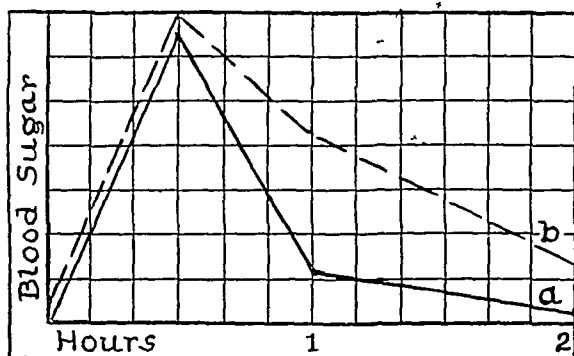


Chart 5—Blood sugar curves of rabbit 20. *a*, curve obtained before the injection of an anaerobic broth culture from the throats of patients with scarlet fever (Aug 8, 1931), *b*, curve obtained twenty-four hours after an injection of an anaerobic broth culture (Aug 27, 1931).

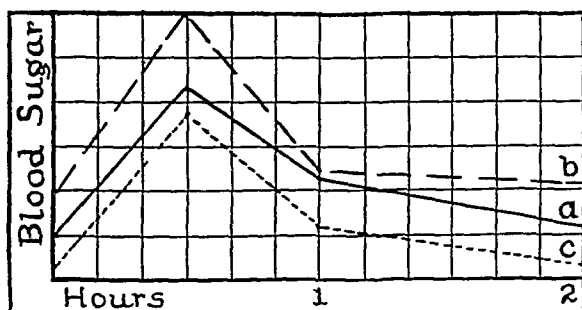


Chart 6—Blood sugar curves of dog III. *a*, curve obtained before infection with typhoid (April 12, 1931), *b*, curve obtained twenty-four hours after the injection of typhoid organisms (June 17, 1931), *c*, curve obtained five weeks after the injection of typhoid organisms (July 29, 1931).

One rabbit which was given paratyphoid B bacillus lived long enough for study. The average amount of dextrose excreted following the injection of the organisms was 0.054 Gm and on one day was as high as 0.106 Gm.

Since the typhoid bacillus gave consistently a greater reduction in tolerance than most other organisms, its effect was tried on two dogs for which carbohydrate tolerance was previously determined in the same manner as for rabbits. Dog 2 lived only seventeen days after experiments were begun, and died two days after the first injection but the

urine contained a trace of sugar on the day following the initial dose. Dog 3 was living nine months after the beginning of the experiment, it was given repeatedly from 0.5 to 7.5 cc of typhoid organisms, and on many occasions the urine gave a positive test for dextrose. The amount of dextrose excreted varied from 0.40 to 0.384 Gm, averaging 0.138 Gm, for the periods following the injection of the organisms. Dextrose tolerance tests disclosed a moderate reduction in tolerance. The blood sugar curve (chart 6) taken twenty-four hours after the organisms were injected revealed a slight reduction in tolerance, whereas that performed after five weeks indicated a slight increase in tolerance.

Postmortem examination of the animals that died (1 rabbit and one dog) revealed no gross alteration of the pancreas, but microscopically there was evidence of degeneration in the islets of Langerhans. This observation, however, is somewhat clouded by the presence of post-mortem change in some of the animals. That toxic injury to the islet cells can occur in both diabetic and nondiabetic patients has been emphasized by Warren and Root<sup>49</sup> who have described necrosis of the islet cells in pneumonia.

#### COMMENT

It is obvious from the results of this work that a temporary glycosuria occurs in acute infections and contagious diseases as well as in experimental infections, 41 per cent of the patients with acute infectious diseases had glycosuria when given sufficient dextrose. Likewise, in experimental infections in animals a similar transient glycosuria has been produced. This is accompanied by an increase in the height of the blood sugar concentration during fasting, and by alterations in the blood sugar curves as shown by the dextrose tolerance tests in animals. Thus it is evident that a decreased tolerance for dextrose occurs in acute infections. The decrease in tolerance may last for several weeks or months; six patients—two with pneumonia and four with scarlet fever—required a restriction of carbohydrate in the diet or the administration of insulin to prevent occasional glycosuria. This decreased tolerance can be improved by supplying insulin additional to that produced in the body. This fact is well illustrated in table 5, in which it is recorded that the excretion of dextrose was reduced to about one third of that when no insulin was given. By increasing the amount of insulin and the frequency of its injections the amount of dextrose in the urine was reduced and in all probability the amount of dextrose excreted could have been reduced to normal had the correct amount of insulin been supplied at the proper time. This is evidence that the toxemia of the disease interferes either with the action or the production of insulin or with both of these factors. By supplying exogenous insulin, which

<sup>49</sup> Warren, S., and Root, H. F. *Am J Path* **1** 415, 1925

restores the carbohydrate tolerance; it would appear that lack of production is probable. This is supported by the experiments of Sweeney<sup>46</sup> on rabbits given injections of diphtheria toxin and in part by the observations of Schwentker and Noel<sup>47</sup> on both patients and animals.

Histologic study of the pancreas in diabetes mellitus failed to disclose *anatomic change in the islets of Langerhans in about 17 per cent of autopsies*, according to Warren<sup>50</sup>. That the lack of insulin production may nevertheless occur in such cases is now freely admitted, and also that this lack of function on the part of the islets may occur in toxemias and infectious diseases is well illustrated by the severity of diabetes during infections and its comparative mildness following recovery from the infection. Thus the action of insulin in improving the carbohydrate tolerance in acute infections is analogous to its similar action in diabetes mellitus. In many instances the severity of the disease and the degree of reduction of tolerance could be correlated, and in patients having one contagious disease following another there was marked reduction of tolerance. This suggests a probable important factor in the etiology of diabetes. The recovery of tolerance following injury by infection is explained by immunity to the infecting organism and by regeneration of the islets of Langerhans. The latter fact has been demonstrated to occur in diabetes in which tolerance has been improved.

#### CONCLUSIONS

1 Glycosuria occurred in 41 per cent of patients with acute infectious diseases. The largest average amount of dextrose was excreted by the patients with influenza and miscellaneous acute infections.

2 This glycosuria is accompanied by a lower carbohydrate tolerance, as shown by dextrose tolerance tests and blood sugar curves both in acute infectious diseases and in experimental infections in animals.

3 Administration of insulin improves the dextrose tolerance in acute infections.

4 This work suggests that in infectious diseases there is often an injury to the islets of Langerhans with a lessened production of insulin.

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<sup>50</sup> Warren, S. The Pathology of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1930, p. 55.

# ASTHMA

## XVI TWO HUNDRED AND THIRTEEN "CURED" PATIENTS FOLLOWED UP FOUR YEARS LATER

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In 1928, an analysis of 213 cases in which the patients were relieved of their asthma for more than two years was published in the ARCHIVES<sup>1</sup>. In that article, a clinical classification of the so-called "cured" cases was presented and a serious attempt was made to define the reason for the "cure". Now, four years later, it is of interest to check up the same 213 cases to see just how permanent the actual "cure" has been and perhaps to throw further light on the mechanism of this "cure". The original article showed the results after two years. Now, an additional four years has been added, and the present article deals with the results six years after the last study and treatment. Very few of the patients have actually been seen or examined at this time, and the following study is based chiefly on letters received from them. If some stress is laid on the incidence of lesions in the nose and throat, it is only because there is reason to believe that such lesions are a handicap in the treatment of asthma.

The gross figures are shown in the accompanying table. It will be convenient to discuss them in accordance with the same clinical classification which was made four years ago.

### EXTRINSIC ASTHMA

*Pollen Asthma*—Five patients are still free from asthma and hay fever, but at least 4 of the original 13 patients have had relapses, with asthma. All 4 have asthma in the summer, but in 2, within the past year or two, additional attacks have developed after colds in the winter. Three other patients, young men, in recent years, have again suffered from hay fever during the ragweed season. Although they have had no asthma with the hay fever, it is obvious that they are far from "cured". They are listed as having asthma again. All 3 have it in the

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<sup>1</sup> Rackemann, F M. Studies in Asthma. II. An Analysis of Two Hundred and Thirteen Cases in which the Patients Were Relieved for More Than Two Years, Arch Int Med 41 346 (March) 1928.

summer, but in 2, within the past year or two, additional attacks have developed after colds in the winter

Lesions in the nose and throat were found originally in only 3 of the 13 cases—infected tonsils in 2 and a cloudy antrum in the third. It is unfortunate that the only patient not heard from is 1 of the 2 with infected tonsils (McG). The other patient with infected tonsils was not operated on, and she (B) is 1 of the 2 who now have trouble in the winter. The patient with a cloudy antrum was originally “cured” in some unknown manner, no specific treatment was given but now he is 1 of those who again have asthma, but only in the summer.

*Infected Pollen Asthma*—Only 5 patients in the original large series were “cured,” a clear illustration of the obstacle which secondary infec-

*Two Hundred and Thirteen “Cured” Cases Followed Again*

Classification	Total Cases	“Cured” 1928	Still “Cured”	Asthma Again	Dead	No Answer
Pollen asthma	70	13	5	7	0	1
Infected pollen asthma	39	5	4	1	0	0
Summer asthma (negative tests)	32	10	4	3	0	3
Animal asthma	60	22	19	1	1	1
Infected animal asthma	13	0	0	0	0	0
Mixed extrinsic	121	22	11	7	0	4
Mixed (negative tests)	57	18	10	7	0	1
Special	53	17	11	5	0	1
Total extrinsic	425	107	64	31	1	11
Bacterial asthma	202	25	16	3	3	3
Bacterial asthma (children)	90	34	23	7	0	4
Reflex (not nose and throat)	66	18	9	4	0	5
Reflex (nose and throat only)	41	11	6	3	0	1
Cardiac	56	1	0	0	1	0
Bronchitis and emphysema	45	3	1	0	1	1
Total intrinsic	499	91	55	17	5	14
Unclassified	150	15	12	1	0	2
Total	1,074	213	131	49	6	27

tion puts in the way of successful treatment. Four of the 5 are still well, and the only patient with trouble is Mrs. W., whose badly abscessed teeth were extracted nearly ten years ago. After the extraction, she remained well for eight years, but two years ago, asthma again developed. It is not unlikely that a new focus of infection has developed in the interim. No foci were observed in the other 4 cases.

*Summer Asthma with Negative Tests*—Only 7 of the original 10 patients have been heard from, and of these, only 4 are still free from asthma. Of the other 3, R., who is now a college student, was operated on for appendicitis in the summer of 1928 and had a bad attack of asthma during his recovery, but during the four years prior to the operation and the three years since then, he has had no trouble. D., who had trouble every June, has done well for a total of six years, except for an isolated attack in June, 1928, and another attack in the

summer of 1930 In C asthma has developed at other seasons besides the summer Unfortunately, the child with the barrel-shaped chest cannot be traced

*Animal Asthma*—This group is an important and fundamental one Unfortunate as it may seem, there is only 1 patient in the total number of 60 who was formerly sensitive to an animal and now has quite lost his sensitiveness This patient is a hostler, who was formerly described as being able to go back to work in the stable The laboratory boy who was sensitive to guinea-pigs and who was reported as being able to tolerate these animals cannot be traced Six patients pronounced themselves free from trouble but unfortunately they did not say whether or not contact with animals occurs in their daily life, and so while their cure is certain in the clinical sense, it is not so certain in the immunologic sense Ten other patients are also free from asthma, but they are only too well aware of their sensitiveness, and their freedom from asthma is due only to the great pains which they take to avoid possible contact with animals Clinically, all of these patients are "cured" The "prize patient" (Agnes C), who was treated successfully with horse dander extract in 1919, is now well and most of the time can tolerate the presence of animals without difficulty, however, if she happens to have a cold in the head at the time of exposure, wheezing does occur Another patient (G) should be noted He was entirely free from asthma after his dog was disposed of in 1925, but last summer he had whooping cough and some asthma followed this disease, although no evident exposure to animals was observed at the time The attack was short, and he is now well again Mary G, a girl of 15, with a typical sensitiveness to horses, was given specific treatment with horse dander extract in 1920, with some success Later she became a nurse, and was free from asthma for several years Unfortunately, she contracted acute bacterial endocarditis and died This leaves only 1 patient (S) in whom the results are not still good When first seen, this patient had foci of infection in her sinuses, tonsils and teeth, and while some of the conditions were treated, it is quite likely that more trouble has developed lately and thus accounts in part for the return of her asthma, which now comes at all seasons of the year in attacks which are usually precipitated by colds in the head

The group of patients with infections with animal asthma should be mentioned only to point out that in the two year follow-up, none of the patients were "cured"

*Extrinsic Mixed and Undentified Cases*—This was the title formerly given to a comparatively large group of patients whose asthma bore a definite relation to changes in the environment, but in whom it was not possible to identify the precise substance to which they were sensitive In most of these cases there was more than one plausible



explanation for the good result. Many of these patients had positive skin reactions to such substances as house dust, mattress hair, feathers and sometimes animal danders and pollens. In the former paper, the whole group was divided into 2 sections, according to the presence or absence of positive skin tests.

Of the 22 patients whose tests were positive and who were "cured," 11 reported that they are still free from asthma, and none of these 11 even suggested that they tend to wheeze when in certain places. On the other hand, there is another group of 7 patients who are essentially well, but nevertheless recognize that they cannot go to certain houses without having a new attack of asthma. Three of them still have hay fever in the ragweed season, although this ragweed was never the sole cause of their trouble. Four of the 7 said that when they have a heavy cold, they are likely to wheeze a little. The question of foci of infection is of interest. In 4 of the 11 favorable cases the patients originally had some evidence of sinus disease, and 2 others had infected tonsils, but none of them had undergone an operation. Among the 7 who are still subject to mild attacks, 2 formerly had some thickening of the sinus membrane.

Four patients of the original group have not been heard from, and 1 of them had a large mucous cyst in the right antrum and a thick membrane in the left antrum, but so far as is known, no operation was performed.

The patients with mixed extrinsic causes who had negative tests are in every way analogous to those in the preceding group. Of the 18 patients originally "cured," 10 reported themselves as still entirely free from asthma. Some of them had moved, but others made no mention of their environment. Of the 8 others, 1 has not been heard from, pulmonary tuberculosis developed in 1, but with no asthma in the interim while another was in rather poor health because of a renal infection which required operation. Her asthma appeared again during the beginning of the infection but since the operation, three years ago, it has disappeared. Four patients admitted that they have attacks of asthma when they have a bad cold. One patient had a relapse, and is now as bad or worse than in the beginning. This woman had formerly reported herself as entirely free from trouble for four years after the time of her marriage and a change of residence, except that at the end of three years she went back to her mother's house and had asthma during the visit. Now she has three small children and has to work hard. She has lost a good deal of weight and severe attacks of asthma have again occurred. Quite likely, the attacks are due to a new hypersensitiveness which she has developed to some substance, perhaps a piece of furniture or other material, in her environment. Foci of infection in the nose and throat were found in 6 of the original 18 cases. No opera-

tions were performed. Three of these patients are now in the group of those perfectly well, the other 3 still being subject to asthma.

*Extrinsic Specials*—The group formerly so designated contained 17 patients with interesting cases. Eleven of them were sensitive to foods. One has not been heard from. Five have completely recovered, not only in the clinical but also in the immunologic sense, since they can now eat the offending foods without trouble. Four children are of special interest. Two of them are still sensitive to fish and eggs and have been careful to avoid these foods for the past ten years. One of them, Robert L., now aged 12, has had slight asthma in September for the past three years (his ragweed test was negative in 1921) while Constance H., now aged 20, has "no asthma as a general rule but if I get tired and at the same time have a cold, it usually develops into a light attack of asthma—Dust aggravates."

John T., who at the age of 5, in 1921, was hypersensitive to wheat and eggs and was relieved by a test-negative diet, now, at 15, eats everything. He wrote, "Rabbits are the only things that bother me." The boy with hypopituitarism, who was sensitive to nuts, still avoids nuts, but he observed that "Horses and cats still bother me." The skin test to horse dander was positive eight years ago, but did not appear to be of clinical importance at that time. Apparently in each of these 4 children a hypersensitiveness to other substances has developed.

One patient has asthma again in severe form. Mrs. L., aged 40, was relieved of her asthma for seven years after following a diet limited to the test-negative substances as found. In 1927, she described herself as "one of the seven wonders of the World." In July, 1931, she wrote that the sinuses were infected and that for the past eight months she had had asthma in severe form.

There are 6 patients sensitive to dust. Two reported themselves as well without making further comment. A third is well, but continues to avoid feathers. A fourth went to California in 1926, and recovered from his asthma. His letter dated March, 1932, is interesting. It contains this note: "I had my nose operated on for polypus—other than that, no trouble." The fifth and sixth patients were young girls whose asthma was due to a hypersensitiveness to feathers. Now, seven and five years later their letters do no mention feathers or asthma, but typical ragweed hay fever has developed in Mrs. W., while Barbara H. has urticaria. It would be interesting to know whether a sensitiveness to some food had developed in the latter patient.

Taking the food and dust cases together, there are 11 patients who are still free from asthma, and all of the others except Mrs. L. are much improved, but it is only too evident that in most of the cases the "cure" is merely a clinical and relative change. Several patients are no longer troubled by the original substance, but they and others neverthe-

less demonstrate their allergy by their capacity to develop sensitiveness to still other materials

Foci of infection were not found in this special group, except in 1 case in which there was frank evidence of sinusitis with polypi. This is the patient who recovered while in California and who had recently had a polypus removed without further asthma. The patients with extrinsic cases in general are far from "cured." The figures show that 31 of the 102 patients with two year "cures" have had relapses, and many of those who are listed as "still cured" depend for their freedom on the careful avoidance of the specific substance. Several interesting points will be discussed later.

#### INTRINSIC ASTHMA

*Bacterial Asthma*—The final end-results among patients with so-called bacterial asthma are comparatively satisfactory. The 59 "cured" patients are divided into 25 adults and 34 children. Among the 25 adults, 3 are dead of other causes, and 3 have not been heard from, but 6 have remained free from trouble since the last follow-up four years ago. Only 3 patients have had asthma in the meantime. One of the 3 is an athletic woman, now 33 years old, who was first seen at the age of 19 on account of asthma which had lasted for one year. At that time she was "cured" after taking benzyl benzoate, her case was described in 1928. For thirteen years she has had no asthma at all, and, in the meantime, she has married and borne two children. Within a year, however, asthma developed, which came on particularly after she played a violent game of squash rackets. On several occasions, the attacks so induced persisted for the following twenty-four hours. There was nothing new about her play for she had been interested in squash rackets for years. The second patient who had a relapse was likewise athletic and as a child had asthma only in association with her sports, particularly tennis. The reason for her improvement was not clear, but the fact is that she did well for about eight years until her marriage. After that event, asthma occurred when the first child was born and reappeared during the second pregnancy. With the third pregnancy, she had asthma once more, having been entirely free since the birth of the second child. The third poor result was also in a woman, who was seen in 1924 at the age of 30. At that time she was given 5 doses of vaccine and thereafter had no further asthma, although she was living at the same address, until the fall of 1930, six years later, when another attack followed a bad cold. Since then, she had been miserable with asthma, which occurred at all seasons of the year and without apparent cause.

Only 1 patient among these 25 had evidence of sinusitis, and she is now free from asthma.

The children, like the adults, have done well. Twenty-three of the total 34 said that they had been free from asthma for the past four years, or since the last note, which often represents a much longer total period.

However, they have not all done well. Four of the children have not been heard from. Five others have occasional spasmodic attacks which are never severe. In 3 of the 5, these attacks occur only during the early autumn, and likely a sensitiveness to ragweed has developed, although the skin tests, which ten years ago showed no reaction to any of the common substances, including the pollens, have not been repeated. In the other 2, mild attacks have occurred within the past year following colds, the relapses having come after free periods of seven and nine years, respectively. Two patients seem to have had real relapses, in that after a free period, which lasted for only two years, their asthma again occurs at frequent intervals and is sometimes of considerable severity. The history however, does not suggest the probable cause. Neither of these 2 patients had foci of infection when first examined.

*Reflex Asthma*—This term was used to define the cases of those patients whose troubles depended on some definite lesion, usually an infectious process elsewhere than in the lung itself. The whole group of 28 cases has been subdivided according to whether the source of trouble was outside the respiratory tract or inside of it, in the tonsils or in the paranasal sinuses. In the group described originally as having asthma dependent on a lesion outside of the respiratory tract, there were 18 patients designated as "cured." Of this number, 9 are still free from asthma four years later. Four still date the time of "cure" from the operation, which in 2 cases was the removal of gallstones, in 1, the extraction of abscessed teeth, and in the fourth (a child), tonsillectomy and appendectomy. Three other patients attributed their improvement to better digestion following the changes in diet which were advised ten years ago. The 9 cases also include 2 former children who are still free from trouble. In these 2 cases, however, the original asthma was never severe and occurred only in slight attacks following colds in children who were thin, frail and in a poor general condition.

Four patients in this reflex group are not "cured," though their asthma is not so troublesome as before. Two patients still show a tendency to wheeze in the winter whenever they catch cold. A man of 45, whose teeth were removed in 1923, gained weight up to 200 pounds (90.7 Kg), he said that he now wheezes on exertion in the winter. A woman, whose appendix, teeth and tonsils had been removed and who was apparently relieved permanently at a later date by vaccines, suffered a return of her asthma, she wrote that a physician wants to operate on her nose and throat. It is unfortunate that 5

patients in this group have not been heard from, especially as all of them did so well at first after the removal of their abscessed teeth or infected tonsils

Diseases of the paranasal sinuses appear to be responsible for the asthma in 10 of the original "cured" "reflex" cases. The operations were on the tonsils in some cases, and on the sinuses in others. One patient cannot be traced. Two children and 1 adult have remained well for more than nine years following tonsillectomy. Marjorie T., aged 12, who had had asthma for three years, was found in 1921 to have badly infected tonsils and many polypi in both nares. Both antrums were dark. At operation, the tonsils and many polypi were removed. Other polypi were taken out from time to time during the next three years, but since 1924 she has had no further asthma, this good result is in spite of the fact that polypi have occasionally formed and been removed. Kenneth B., a poorly nourished, tired, pale boy of 6 with persistent asthma of some severity had infected tonsils which were taken out at the age of 7. He is now 15 years of age, weighs 188 pounds (85.3 Kg) and is 6 feet tall (182.9 cm). There are at least 3 patients who have had operations on the sinuses with good results which appear to be permanent. Mrs. D., a woman of 63, who had had asthma since the age of 60, had her ethmoiditis and antrums operated on, and in the nine years since then she has had no asthma, although she is living in the same place. Mrs. W., aged 43, who had asthma for eight years and polypoid ethmoiditis, has been entirely well for eight years since an operation. Mrs. R., aged 54, has a similar history. On the other hand, Mrs. R., aged 55, whose sinuses were operated on in 1921, caught a severe cold in 1930, and since then has had occasional slight attacks of asthma, which fortunately are never severe. Much the same story applies to 2 other patients who are infinitely better, but who still may have asthma with colds or with sudden changes in temperature. One patient has been lost from observation.

*Cardiac Asthma and Chronic Bronchitis with Emphysema*—These conditions have poor prognoses, as is shown by the practical absence of "cured" cases in the series of 1928. At that time, too, the diagnosis of cardiac asthma was based on even less definite evidence than now. Today, two important points in the diagnosis of cardiac asthma are recognized: (1) the age of onset is past 50, and (2) the attacks are precipitated by exertion or excitement. In a patient, aged 65, who had had severe asthma since the age of 17, symptoms of decompensation and angina pectoris subsequently developed. Today her heart disease would be regarded as something independent of her asthma, and she would not be described as having cardiac asthma. She died at the age of 71 of angina pectoris, she had no real wheeze for the past ten years.

Three patients were formerly described as "cured" despite their chronic bronchitis and emphysema. Two of them were women who did well for two and five years, respectively, up to 1928, after taking potassium iodide. The younger patient, aged 53, has continued well to the present time, or for a total of six years, while the older one, aged 61, died suddenly after a free period of eight years. The Jewish tailor is "lost."

*Unclassified Asthma*—This heading is necessary. Of 15 patients "cured" in 1928, 12 are still free from trouble, though 1 of the 12 has nasal polyp<sub>i</sub> which must be removed about once each year. One patient who was supposedly "cured" by intravenous doses of sodium iodide did well for only two years and now is ill again. The remaining 2 patients cannot be traced.

#### COMMENT

The results of this study show that the longer a series of patients with asthma is studied, the more evident it becomes that true "cure" is a doubtful prospect even though many patients remain symptom-free for long periods. The number of "cured" cases, which was 213 in 1928, has been reduced to 131, or 12 per cent, of the original total of 1,074 cases. The dictum "once an asthmatic, a patient is usually a potential asthmatic for the rest of his life," as pronounced by Vander Veer,<sup>2</sup> seems to be borne out by these findings.

Why is treatment so difficult? Why are the results so poor? As said four years ago, the results in the extrinsic group show that cure has been accomplished by removal of the trigger which fired the attack, but obviously the gun remains loaded in most, and probably in all, cases. Evidently fundamental allergy is a remarkably persistent trait. The conception of the "capacity to develop sensitiveness" as a supplement to von Pirquet's conception a "capacity to react" (*Reactionsfähigkeit*) seems justified by the observation of patients over periods long enough to see that they tend to develop sensitiveness to new substances in their environment. It is the capacity which is fundamental. Its nature is quite unknown.

The influence of a chronic sinus infection is always interesting and difficult to analyze. Whether more patients with sinusitis have asthma than do not have asthma is uncertain, but it is evident that sinusitis is a common finding in asthma. Acute colds and acute sinus infections can cause asthma in short attacks, which last for the duration of the infection. Furthermore, chronic sinus infections can cause asthma, which then is also chronic, and in a few cases, the chronic asthma is relieved for long periods by operations on the sinuses. In these cases, the sinusitis appears to be the primary exciting cause of the asthma.

2 Vander Veer, A, Jr. The Present Status of the Treatment of Hay Fever and Asthma, *Am J M Sc* 164 97, 1922

In other cases, however, such good results have not followed radical treatment, and in still others, clinical recovery has occurred even though nasal polypi and other evidences of sinus infection were still present

Finally, there are cases in which the sinus lesion is a complication which adds to the primary cause to produce a summation or total which in turn leads to asthma. In these cases, neither the extrinsic factor alone nor the infection alone is sufficient to produce symptoms which depend on the presence of infection at the time of exposure to the foreign substance

Can the high incidence of sinusitis be correlated with the capacity to develop sensitiveness? Is it possible that allergic tissue reactions tend to hold the infection while immune serum reactions tend to destroy it? The thought is attractive. So far one can only speculate on it. Progress will be more rapid as one learns that in asthma the fundamental problem lies not in the sensitiveness to any particular protein or in the incidence and treatment of nasal disease, but in the study of the capacity to develop sensitiveness to foreign substances. Doubtless this capacity is inherited and may well be, as Morris H. Kahn<sup>3</sup> suggested, "rooted in the biologic and physico-chemical structure of the chromosomes."

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3 Kahn, M. H. The Present Status of Curability of Bronchial Asthma, *Arch. Int. Med.* **39** 621 (May) 1927

# HYPERPROTEINEMIA DUE TO BENCE-JONES PROTEIN IN MYELOMATOSIS

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Elevation of the serum protein content, except in dehydration, is observed rarely in clinical practice. Even with marked loss of fluid from the body the increase of protein in the blood usually is not great. True hyperproteinemia is exceedingly rare. Loeper, Forestier and Tonnet<sup>1</sup> found the serum protein to be 11 mg per hundred cubic centimeters in one case of malignant tumor of the kidney. Wu<sup>2</sup> reported that one patient with kala-azar had a serum protein of 10.52 mg and a serum globulin of 9.06 mg. The highest serum protein content observed by Rowe<sup>3</sup> was 10.4 mg in a patient suffering from glandular enlargement. However, no known clinical syndrome shows constantly an increase in the protein of the blood.

Few studies on proteins of the blood in patients with multiple myelomas have been reported. Ellinger<sup>4</sup> demonstrated qualitatively the presence of Bence-Jones protein in blood and in ascitic fluid, as did Askanazy<sup>5</sup> in blood and in pericardial and pleural fluid. Weber<sup>6</sup> found it in pericardial fluid, and Hewitt<sup>7</sup> in the blood of patients suffering from multiple myelomas. In 1917, Jacobson<sup>8</sup> found and determined quantitatively a

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From the Cleveland Clinic

1 Loeper, M., Forestier, J., and Tonnet, J. *Chemistry of the Blood in Cancer*, Presse méd **29** 333, 1921

2 Wu, H. *New Colorimetric Method for Determination of Plasma Proteins*, J Biol Chem **51** 33, 1922

3 Rowe, A. H. *The Albumin and Globulin Content of Human Blood Serum*, Arch Int Med **18** 455 (Oct) 1916

4 Ellinger, A. *Das Vorkommen des Bence-Jonesschen Körpers im Harn bei Tumoren des Knochenmarks und seine diagnostische Bedeutung*, Deutsches Arch f klin Med **62** 255, 1899

5 Askanazy, S. *Ueber die diagnostische Bedeutung der Ausscheidung Bence-Jonesschen Körpers durch den Harn*, Deutsches Arch f klin Med **68** 34, 1900

6 Weber, F. P. *Multiple Myelomatosis with Bence-Jones Protein in the Urine*, Am J M Sc **126** 644, 1903

7 Hewitt, L. F. *Bence-Jones Proteins*, Biochem J **23** 1147, 1929

8 Jacobson, V. C. *A Case of Multiple Myelomata with Chronic Nephritis Showing Bence-Jones Protein in Urine and Blood Serum*, J Urol **1** 167, 1917



large amount of Bence-Jones protein in the blood of a patient suffering from myelomatosis and severe chronic nephritis. The total content of protein in the serum of this patient was not determined, but evidently was high, since the value for the Bence-Jones protein alone was 7.87 mg per hundred cubic centimeters. Jacobson noted precipitation of the protein on inactivating (by heating for one-half hour at 56 C) the serum in preparation for a Wassermann test. This phenomenon was observed by Short and Crawford<sup>9</sup> also.

Recently Perlzweig, Delrue and Geschickter<sup>10</sup> reported a single case of myelomatosis in which the total protein in the plasma amounted to 13.84 mg per hundred cubic centimeters. They precipitated a fraction of the protein from this serum by heating to 56 C, but this remained insoluble at the boiling point. These authors concluded that only a small amount of Bence-Jones protein was present in the blood serum of their patient, and that the high value for protein was due to a physiologic reaction in response to the introduction of this small amount of foreign protein. Hewitt<sup>7</sup> called attention to the fact that different samples of Bence-Jones protein vary greatly in solubility and in other physical and chemical properties. Hopkins and Savoy<sup>11</sup> found that this variation in solubility is dependent on the acidity and the salt content. To us, it seems more than probable that the increase in total serum protein in the case reported by Perlzweig, Delrue and Geschickter was due to the presence of Bence-Jones protein. Since there are no cases reported in the literature on hyperproteinemia proved to be due to Bence-Jones protein, it seems worth while to report two such cases that we have had under observation recently.

In the first case, in view of the high amount of total protein in the blood serum and the report of precipitation of the blood serum during inactivation for the Wassermann test, special studies of the serum for Bence-Jones protein were made. Several times, large amounts of a protein precipitating at 56 C and almost completely dissolving at the boiling point were demonstrated, and quantitative estimations were made. Two procedures were used in analyzing this protein quantitatively. The undiluted serum, the protein content of which had been determined, was heated in a water bath at 56 C. In half an hour cold distilled water was added, the mixture was centrifugated, and the washings were saved. The precipitate was washed several times in this

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9 Short, J. J., and Crawford, J. R. Bence-Jones Protein in Blood Serum Leading to Detection of Multiple Myelomatosis. Report of a Case, *J. Lab. & Clin. Med.* **14** 1092, 1929.

10 Perlzweig, W. A., Delrue, G., and Geschickter, C. Hyperproteinemia Associated with Multiple Myelomas, *J. A. M. A.* **90** 755 (March 10) 1929.

11 Hopkins, E. G., and Savoy, H. A Study of Bence-Jones Protein and of the Metabolism in Three Cases of Bence-Jones Proteinuria, *J. Physiol.* **42** 189, 1911.

manner The total protein in the washings was determined, and the amount of protein precipitated was calculated by subtracting the total protein in the washings from the total protein of the original serum The precipitated protein also was suspended in distilled water and was determined quantitatively The amounts of Bence-Jones protein as determined by these two methods corresponded closely Hence we feel that the values obtained must be approximately correct

Perlzweig, Delrue and Geschickter suggested that Jacobson's findings might be explained on the basis of precipitation of a large amount of euglobulin at 56 C, with the occlusion of a small amount of Bence-Jones protein in the precipitate This explanation certainly is not correct in our cases, since the precipitate was almost completely soluble at the boiling point, this would not be possible if the major part of it were globulin, although it is possible that in our experiments a small amount of globulin was carried down with the precipitation of Bence-Jones protein Control studies with the same technic on normal serums gave no precipitate In the cases reported here, most of the Bence-Jones protein came down in the euglobulin fraction on fractional precipitation with sodium sulphate This is what might be expected, since the close relation of Bence-Jones protein to globulin has been emphasized in the careful chemical and physical study made by Hopkins and Savory<sup>11</sup> Many of the properties of a solution of Bence-Jones protein at the boiling point and of typical blood globulin at room temperature are identical Hopkins and Savory concluded "The fundamental difference between Bence-Jones protein and globulin is the difference of temperature factor involved in their equilibrium with salts What is special in the temperature relation is the basis of what is special in the physical chemistry of the Bence-Jones protein"

#### REPORT OF CASES

CASE 1—A white man, 64 years of age, was first seen in the Cleveland Clinic on June 23, 1931 He complained of stiffness in the neck which had been present for three months Two weeks before he consulted us, while playing golf, he had begun to have pain in the lower part of the back which confined him to bed It was a dull pain radiating anteriorly around to the abdominal muscles and was relieved considerably by the application of heat The patient's clinical history previous to the onset of these symptoms seemed irrelevant, however, at times he had felt some stiffness and pain in various joints and muscles

General physical examination showed no significant findings except for definite limitation of abduction and rotation in the left shoulder and of extension in both knees The lumbar spine was flat, and there was spasm of the lumbar muscles The patient had great difficulty in rising from the prone position

Examination of the blood revealed marked anemia The erythrocytes numbered 3,240,000 and the leukocytes 5,400 The urine had a low specific gravity, a slight trace of albumin and hyaline and granular casts The Wassermann test of the blood could not be made, because a precipitate was formed in the serum during inactivation (56 C)

Roentgen examination of the lumbar spine showed marked generalized atrophy of the spine and lipping of the vertebrae. The patient was put to bed and physical therapy was instituted, but he became progressively worse. Even with rest in bed the severe pain with movement persisted. At times the pain in the chest and in the lower part of the lumbar area was extremely intense.

On account of continued pain the patient was admitted to the Cleveland Clinic Hospital on Oct 10, 1931. Further studies at that time revealed the correct diagnosis of myelomatosis. The clinical course was steadily downward. The anemia became more pronounced, and the pain accompanying movement increased. Roentgen examination of the spine showed compression of the tenth dorsal vertebra. This was considered by the roentgenologist to be due in all probability to metastatic malignancy. The generalized atrophy of the bones was striking, but no discrete multiple punched-out areas typical of myeloma were found. The long bones were not involved. The urine was examined repeatedly, but no Bence-Jones bodies were found. No primary malignant tumor was revealed, although a careful clinical search was made. A biopsy of the twelfth rib was made, but the only finding of significance was hyperplasia of the bone marrow. Later spontaneous fracture of several ribs occurred when the patient was moved in bed. The anemia

TABLE 1—*Results of Chemical Examination of the Blood (Case 1)*

Date, 1931	Nonprotein Nitrogen, Mg	Urea, Mg	Creatinine, Mg	Uric Acid, Mg	Calcium, Mg	Phosphorus, Mg	Chloride, Mg
Oct 13	36.4			4.8	14.0	4.01	
Oct 28					13.5	4.57	
Nov 1					13.2	4.60	
Nov 7		45	1.4	4.6	15.5	2.60	544
Nov 21		81					
Nov 25		210			12.2	8.00	544

continued to increase, and bilateral pleural effusion and terminal bronchopneumonia developed. This caused the patient's death on Nov 25, 1931, five months after his first admission to the clinic.

All the bones examined at necropsy showed marked loss of calcium salts, thinning of the cortex and atrophy of the trabeculae. The cortex of the vertebrae was especially thin. The marrow spaces as well as the entire body of the vertebrae were filled with soft, friable, very cellular material. Only in the twelfth dorsal vertebra was a circumscribed area of infiltration found, this was filled with white, soft, cellular material. There was no myelomatous or other neoplastic infiltration of the periosteum or surrounding tissues in any of the bones examined. Stained smears from the marrow showed microscopically a predominance of large cells simulating plasma cells. The bone marrow in the ribs and manubrium was hyperplastic.

Specimens of blood from the heart, of spinal fluid and of pericardial and pleural fluids were obtained at autopsy for chemical study. The clinical diagnosis was myelomatosis, although the roentgenographic findings were not typical and no Bence-Jones bodies could be demonstrated in the urine.

The first chemical examination of the blood was made on Oct 10, 1931, the day of the patient's admission to the hospital. The value for nonprotein nitrogen was normal (36.4 mg), that for uric acid was elevated (4.8 mg), that for phosphorus was above normal (4.01 mg), and that for calcium was very high (14 mg). The amount of urea in the blood gradually rose, reaching 210 mg per hundred cubic centimeters before the patient's death. The level of calcium in the

blood was constantly high, varying from 12 to 15.5 mg. At the time of the patient's death the phosphorus measured 8 mg (table 1).

A specimen of spinal fluid obtained on Nov. 10, 1931, showed 2.9 mg of protein and 5.8 mg of calcium per hundred cubic centimeters. No Bence-Jones bodies could be demonstrated in this specimen or in a second specimen obtained at necropsy. The result of the dextrose tolerance test was normal.

The protein content of the serum was determined repeatedly and constantly found to be high. The elevated protein content was due entirely to an increase in the globulin portion. The increase in the globulin might be accounted for by the presence of Bence-Jones protein. The highest value for total protein was 13.78 mg per hundred cubic centimeters, and the lowest was 10.06 mg. The globulin portion varied from 6.53 to 11.34 mg. The Bence-Jones protein in the blood varied from 7 to 9 mg. At autopsy, the pleural fluid contained 3.4 mg and the pericardial fluid 2.5 mg of Bence-Jones protein. The results of the studies of protein are shown in table 2.

In view of the increased calcium in the blood the possibility of hyperparathyroidism was considered. The amount of phosphatase in the plasma, determined

TABLE 2—*Estimations of Protein (Case 1)*

Specimen	Date, 1931	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent	Bence Jones Protein, per Cent
Blood	Oct. 13	12.25	2.99	9.26	
	Nov. 1	10.94	2.70	8.24	
	Nov. 7	13.78	2.44	11.34	
	Nov. 16	11.93	2.55	9.38	8.75
	Nov. 17	10.47	1.25	9.22	7.85
	Nov. 21	10.72	3.25	7.47	7.85
	Nov. 25	10.06	3.53	6.53	
	Autopsy	10.40			7.40
Pericardial fluid	Autopsy	5.40			2.60
Right pleural fluid	Autopsy	8.50			5.10

according to the method of Kay, was normal (0.12 units per hundred cubic centimeters).

CASE 2—A white woman, 49 years of age, was seen first in the clinic on July 29, 1931, she was complaining of pain in the lower part of the lumbar region and of weakness in the legs. She stated that she had been well until November, 1930, later she began to have a dull pain in the right flank which remained localized and was never severe. At that time she was studied at another hospital, where a diagnosis of enlarged kidney was made. Later the pain became localized in the upper part of the right lumbar region and was aggravated by any movement. The weakness in the legs had been progressive and had necessitated the use of a cane and crutches. She stated that her physicians had observed albuminuria for some time. She had lost 25 pounds (11.3 Kg.) in weight since the onset of the illness.

On general physical examination the patient's temperature and pulse rate were normal, she weighed 145 pounds (65.8 Kg.), and her blood pressure was 135 systolic and 80 diastolic. Examination of the heart and lungs revealed no abnormality. The abdominal muscles were tense. There was practically no motion in the spine. There were marked scoliosis and tenderness on pressure over the spine in the lumbar region and the lower part of the thoracic region. Voluntary movements of the muscles, especially of the legs, were weak.

Roentgen examination showed widespread destructive tumors typical of multiple myeloma in the vertebrae in the ribs, and in the shoulder and hip girdles. The

eleventh dorsal and the first and fifth lumbar vertebrae were compressed. The skull and long bones also showed areas of destruction due to multiple small tumors.

The specific gravity of the urine varied from 0.012 to 1.020. Albumin in varying amounts was constantly present. Bence-Jones protein was detected in the urine at every examination. One quantitative determination of Bence-Jones bodies showed the amount to be 0.56 mg per hundred cubic centimeters. Marked anemia was present. The erythrocyte count was 2,840,000, the leukocytes numbered 5,400, with a normal differential count, and the amount of hemoglobin was 58 per cent (9 Gm). The blood sugar was found to be 87 mg per hundred cubic centimeters, the urea, 24 mg, the chlorides, 594 mg, the calcium, 11.15 mg, and the phosphorus, 4.28 mg. The spinal fluid contained 110 mg of protein per hundred cubic centimeters, but no Bence-Jones bodies could be demonstrated. A precipitate was formed in the serum during the process of inactivation for the Wassermann reaction.

The first estimation of protein in the blood showed the total amount to be 11.37 mg per hundred cubic centimeters, of which 2.44 mg was albumin and 8.93 mg globulin. A later complete study of the protein revealed the following: total protein, 10.02 mg; albumin, 2.30 mg; globulin (total), 7.72 mg; euglobulin, 6.32 mg; pseudoglobulin I, 0.66 mg; pseudoglobulin II, 0.74 mg; and Bence-Jones

TABLE 3—*Results of Chemical Examination of the Blood (Case 2)*

Date	Calcium, Mg per 100 Cc	Phos- phorus, Mg per 100 Cc	Serum Protein, per Cent						Bence Jones Protein
			Total	Albu- min	Glob- ulin	Euglob- ulin	Pseudo- globulin I	Pseudo- globulin II	
7/29/31	11.15	4.28	11.37	2.44	8.93				
7/30/31			10.02	2.30	7.72	6.32	0.66	0.74	4.13

protein, 4.13 mg. The important chemical findings in the blood are summarized in table 3. The patient's condition did not change during her stay of ten days in the hospital.

#### COMMENT

In these two cases the amount of total protein was high, and the increase was proved to be due to the presence of a large amount of Bence-Jones protein. In each instance there was a precipitation of the foreign protein on inactivation of the serum for the Wassermann test. In the Cleveland Clinic other cases of multiple myeloma have been studied without the finding of hyperproteinemia or Bence-Jones bodies in the serum. No logical explanation for the occasional finding of Bence-Jones protein in the blood is apparent. Jacobson thought that a complicating nephritis, preventing excretion, was responsible for the Bence-Jones proteinemia and the absence of the protein in the urine of his patient. In the two cases reported here there was no evidence of disease of the kidneys to explain the hyperproteinemia. Aside from its diagnostic value the presence of Bence-Jones bodies has no clinical significance so far as is known. Owing to the protein content, the osmotic pressure of the serum is increased somewhat, but not greatly,

since the osmotic pressure exerted by globulin is only one-fourth as great as that of albumin

The blood calcium was high in both of our cases. In case 1 there was evidently a widespread loss of calcium salts from the bones. In case 2 only focal areas of bone destruction were present. The increase of calcium in the blood is easily explained on the basis of the decalcification incident to the widespread osseous lesions of the disease.

#### SUMMARY

Two cases of myelomatosis with a high content of protein in the blood serum are reported.

The increase in protein was in the euglobulin portion of the globulin.

Bence-Jones protein in large amounts was demonstrated in the serum of both patients.

The increase in the total protein in the blood was proved to be due to the presence of large amounts of Bence-Jones protein.

A high level of calcium was found in the blood of both patients, in one, the roentgenograms showed only a generalized atrophy of bone, in the other, there were the characteristic punched-out areas of bone destruction.

# MATURING EFFECT OF ROENTGEN RAYS ON BLOOD-FORMING CELLS

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There are numerous views as to the nature of the action of roentgen rays on living tissues. In general, it is felt that small doses "stimulate" and large doses "depress." After the therapeutic use of large doses, death or a decrease in the size of the exposed tissue follows. Whether this action is one of a toxic necrosis of tissue directly, a mechanism disturbing the cell division or an increase in the rate and intensity of the normal processes in the life of the cell is a matter of discussion.

For the study of the effect of roentgen rays on living tissue, the blood offers admirable material. The polymorphonuclear leukocytes may be recognized morphologically in twelve or more stages in the course of their life history, and at least five or six definite stages in the maturation of a red blood cell can be identified. This enables one to study the effect of irradiation with relation to the rate of maturation, so that it can be noted whether the cells reach maturity and die of senility, or whether there is a toxic necrosis, with death in the stage during which the cell was irradiated.

The material for study consisted of patients with various types of leukemia, lymphoblastoma or cancer, the data obtained representing observations on over 923 patients. Studies of the blood were made before and after treatment over long periods, occasionally with many observations at short intervals.

Of the cells that grow in the bone marrow, the youngest stage seen in the blood under pathologic conditions is that of the primitive myeloblast. In the bone marrow this is a small cell, which is slightly larger than a red blood cell, and which resembles a lymphocyte in certain superficial aspects. This cell normally grows larger and becomes a myeloblast. The next stage is that of the myelocyte, the largest cell of the series. The myelocyte shrinks and forms the metamyelocyte, and, as the shrinking process continues, the nucleus becomes indented, finally, distinct lobes appear, and the cell becomes a polymorphonuclear leukocyte. The

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Presented at the symposium on the "Biological Action of X-Rays" before the American Association for the Advancement of Science, the American Roentgen Ray Society, the American Society of Bacteriologists and the American Chemical Society at Syracuse, N. Y., June 24, 1932.

myeloblasts and the primitive myeloblasts have the power to divide and produce new myeloblasts or to mature and produce adult polymorphonuclear leukocytes. When a cell of the bone marrow is stimulated, it does one of two things. It may divide and reproduce rapidly (myeloblasts and primitive myeloblasts), or it may run through the rest of the stages of maturation and become an adult cell. When a person is exposed to roentgen rays, the myeloblasts reproduce more myeloblasts (an undesirable effect) and the myelocytes mature to polymorphonuclear leukocytes (a desirable effect).<sup>1</sup> This is readily seen when careful studies on the blood are made at frequent intervals before and after roentgen treatment.

A similar maturation process takes place in the red blood cells. The youngest red cell is a nucleated form, normally confined to the bone marrow. This matures into the reticulocyte, then into the granule and then into the mature erythrocyte. Immediately (less than one-half hour) after adequate roentgen therapy, the number of granular red blood cells increases, showing that reticulocytes have been matured to the next older stage. Then the reticulocytes increase, showing that the nucleated cells have been stimulated to mature quickly to the reticulocytic stage. As days pass the reticulocytes decrease in number and mature into the granule stage, and the number of these cells again rises. Then the number of mature cells increases.<sup>2</sup> This observation is well shown by a study of patients with cancer, leukemia and lymphoblastoma, as well as by the ability of roentgen irradiation (Minot and Lee,<sup>3</sup> and others<sup>4</sup>) to induce a remission in pernicious anemia or improvement in other types of anemia. Pernicious anemia is characterized by gross immaturity of the red blood cells in the bone marrow, and the stimulus of the roentgen ray makes the cells mature.

Similar evidence may be gathered from a study of the lymphocytes. The youngest stage reaching the peripheral circulation under pathologic conditions is the primitive lymphoblast, which closely resembles the

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1 Isaacs, R. Blood Changes in the Leukemias and Lymphomata and Their Bearing on Roentgen Therapy, *Am J Roentgenol* **24** 648, 1930.

2 Isaacs, R. Effect of Roentgen Ray Irradiation on Red Blood Cell Production in Cancer and Leukemia, *Am J M Sc* **171** 20, 1926.

3 Minot, G. R., and Lee, R. I. Treatment of Pernicious Anemia, Especially by Transfusion and Splenectomy, *Boston M & S J* **177** 761, 1917.

4 Bucky, G., and Guggenheimer, H. Steigerung der Knochenmarksfunktion durch Röntgenreizdosen, *Klin Wchnschr* **1** 11, 1922. Dazzi, A. Morphological Changes of the Blood, Following Irradiation of the Splenic Area, with So-Called Stimulating Doses, *Radiol med* **11** 529, 1924. Faberi, M. A Case of Severe Anemia of Aplastic Type Treated with Radiotherapy, *Policlinico (sez prat)* **31** 1229, 1924. Tomanek, F. Results of Radium Treatment of Pernicious Anemia, *Časop lék česk* **63** 549, 1924. Yousenburg, A. Roentgen Therapy in Blood Diseases, *Vestník rentgen i radiol* **3** 18, 1924.



primitive myeloblast in its appearance and its behavior to roentgen irradiation. The cell normally is confined to the lymphoid tissue and matures thus into the lymphoblast, the large lymphocyte, the medium-sized small lymphocyte and, finally, into the adult small lymphocyte. Exposure to roentgen radiation during the primitive lymphoblastic and the lymphoblastic stages causes the cells to reproduce with the rapid production of additional primitive lymphoblasts. As the bulk of the cells are in this stage in acute lymphatic leukemia and in the terminal stage of chronic lymphatic leukemia, roentgen irradiation does not lower the white blood cell count appreciably, and frequently aggravates the condition. When the bulk of the cells are lymphocytes of medium or small size, roentgen irradiation stimulates them to grow old, and they are excreted into the gastro-intestinal tract (Isaacs and Danielian,<sup>5</sup> Bunting and Huston<sup>6</sup>). Therefore, the quickest response in the reduction of the white cell count after adequate therapy occurs when the bulk of the cells are lymphocytes of small and medium size (that is, relatively mature), and the response is but slight when the bulk of the cells are large lymphocytes and lymphoblasts. The stimulation of young cells to grow older results in an initial increase in the number of lymphocytes in the blood stream before the decrease starts. This is best seen when small doses of radiation have been used.<sup>7</sup>

The monocytes, especially those seen in monocytic leukemia, go through a similar process of stimulation and development, although at a much slower rate.

While it has generally been considered that "small doses stimulate and large doses depress," in reality, all doses are stimulating, the larger doses, however, cause such a rapid rate of growth that the normal end is soon reached, and the cellular activities then appear to be "depressed." The maturation stimulating effect of roentgen irradiation is shown in several ways. Young cells stained while living with Janus green and neutral red show more granules stained with the former than with the latter dye. In older cells the neutral red granules predominate. In cells exposed to roentgen rays and stained supravitaly with Janus green and neutral red, the granules stained with the latter dye increase in number.

5 Isaacs, R., and Danielian, A. C. Maintenance of Leukocyte Level and Changes During Irradiation. Study of the White Blood Corpuscles Appearing in the Saliva and Their Relation to Those in the Blood, *Am J M Sc* **174** 70, 1927.

6 Bunting, C. H., and Huston, J. Fate of the Lymphocyte, *J Exper Med* **33** 593, 1921.

7 Taylor, H. D., Witherbee, W. D., and Murphy, J. B. Studies on X-Ray Effects. I Destructive Action on Blood Cells, *J Exper Med* **29** 53, 1919. Thomas, M. M. Taylor, H. D., and Witherbee, W. D. Studies on X-Ray Effects. II Stimulative Action on the Lymphocytes, *J Exper Med* **29** 75, 1919.

and those stained with Janus green decrease<sup>8</sup> This indicates that the cells grow older rapidly when exposed to the effects of radiation

A second phenomenon which indicates that roentgen irradiation causes the blood cells to mature and to die of senility or to be disposed of as mature cells normally are, instead of being "killed" by the therapy, is observed in a study of the saliva Normally when a polymorphonuclear leukocyte matures and runs through its life course, it reaches the capillaries of the mucous membranes of the gastro-intestinal tract, especially those of the mouth, and works its way through the lining into the mouth cavity by its own powers of locomotion<sup>5</sup> The myeloblasts and myelocytes cannot do this, so they accumulate in the blood stream and, under abnormal conditions, as in myelogenous leukemia, enter the peripheral circulation, they are removed only when they mature or die As soon as a myelocyte matures into a metamyelocyte and young polymorphonuclear leukocyte, it has the power of invading the mucous membrane (diapedesis, leukopedesis) In a normal person about from 5 to 150 leukocytes per cubic millimeter are washed up by the saliva as it bathes the mucous membranes<sup>5</sup> After roentgen therapy (in patients with cancer or leukemia or in normal animals) the number increases in the saliva, reaching 10,000 per cubic millimeter or more, especially in chronic myelogenous leukemia<sup>5</sup> This indicates that following the treatment, increased numbers of immature cells are stimulated to become mature enough to wander through the mucous membranes There are first an increase in the blood count after therapy and then a decrease in the number of cells in the peripheral circulation, and the white cell count approaches nearer normal, with a decrease in the number of immature cells (myelocytes and metamyelocytes)<sup>9</sup> However, the number of myeloblasts may not be reduced, and at times is increased They have been stimulated not to mature, but to divide and reproduce This may not be evident in the peripheral circulation, because the presence of a myeloblast in the blood stream is abnormal, but it is well shown in studies of the bone marrow, where the myeloblasts grow The number of mitotic figures in dividing cells increases in the bone marrow in from twelve to twenty-four hours after irradiation and decreases rapidly after this<sup>10</sup> The myeloblasts may fill the spaces of the bone marrow and crowd out all other cells When the bulk of the cells are in this state in the bone marrow, the patient is said to be refractory to roentgen therapy, because

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8 Prigosen, R. E. Vital Staining of Tumor Cells After X-Ray, *J. Cancer Research* **8** 305, 1924

9 Minot, G. R., and Spurling, R. G. Effect on the Blood of Irradiation, Especially Short Wave Length Roentgen-Ray Therapy, *Am. J. M. Sc.* **168** 215, 1924

10 Mottram, J. C. Histological Changes in the Bone-Marrow of Rats Exposed to Radiations from Radium, *Arch. Radiol. & Electroth.* **25** 197, 1920

these cells cannot be stimulated to mature and be lost from the body as are the adult cells. The roentgen radiation, however, does not kill them, but stimulates further growth. When small doses are applied over long periods, the number of germinating cells decreases, and aplastic anemia develops. This is always preceded by a period of hyperplasia in which the cells have been stimulated to abnormal growth until the marrow becomes "exhausted."

The stimulation of maturation of the white blood cells is further shown by a study of the age of polymorphonuclear leukocytes in the peripheral circulation. The youngest cells have a single round nucleus, in the older stage, it is a band form, which becomes constricted into two lobes, and then into three, four, five, six or more lobes. When these types of cells are stimulated to grow older, the number of lobes in the nucleus increases. Kennedy and Grover<sup>11</sup> have shown that after roentgen irradiation of normal rabbits the number of cells with one lobe reaches the maximum in three and one-fourth hours, with two lobes in from one to two days, with three lobes, in from four to five days, with four lobes, in from six to seven days and with five lobes and more, after seven days. In other words, within three and one-fourth hours after therapy the number of myelocytes maturing into metamyelocytes begins to increase, and the process continues throughout the rest of the developmental cycle during the following days.

A careful study of the kinds of polymorphonuclear leukocytes during the first fourteen hours after roentgen irradiation shows that the number of one-lobed cells increases rapidly, starting during the first hour, the maximum being reached in three and one-fourth hours, and that the number remains elevated, with only a slight decrease, during the first fourteen hours. In contrast to this, the number of cells with two lobes decreases slowly but definitely, and the number with three, four and more lobes decreases abruptly and markedly during the first hour.<sup>11</sup> The reason for this is evident. The powers of movement of the one-lobed cells through the mucous membranes (leukopedesis) is feeble compared to that of the others,<sup>5</sup> and they do not appear in great numbers in the mouth, those with two lobes can move more rapidly, whereas those with three or more lobes have active powers of locomotion and quickly migrate from the circulation.

There is always a latent period between the time of exposure to the radiation and the therapeutic results. This period represents the length of time that it takes for a cell to mature, to behave as an adult tissue and to suffer its fate. The period varies with the kind of cell and the stage of development at the time of irradiation (the time required for a

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<sup>11</sup> Kennedy, W. P., and Grover, C. A. Studies on the Arneth Count. VIII. The Deflection of the Count by X-Rays, *Quart J Exper Physiol* **18** 79, 1927.

reticulocyte to become a granular red cell is fifteen minutes, for a myelocyte to become a metamyelocyte, about three and one-fourth hours, for a carcinoma cell in the breast to mature, about two weeks) as well as with the effective dose

Throughout the changes that take place in the blood cells, no new stages or types appear. There is an orderly progression to either increased cell division or development to maturity. All of the changes after irradiation are steps that appear normally in the life history of the healthy cell, and the changes occur in an orderly manner, exactly as a normal cell grows, but possibly at an accelerated rate. There is no evidence of degeneration of cells before they reach maturity. After this the fate of the cells is similar to that of the normal cells of the same type. Clinically, the blood of a patient with chronic leukemia may be restored to normal either by intensive irradiation with the maximal dose that the skin will permit or by irradiation at frequent intervals with small doses. In the former case, however, the response is more rapid and the normal blood picture is reached days or weeks sooner than when small doses are given. With the small doses there is a greater tendency for the myeloblastic or lymphoblastic tissue to be stimulated to active growth, so that the so-called "refractory" stage of the disease (in reality the stage when most of the cells are blasts) is reached more quickly.

The same process appears to take place in other irradiated tissue, such as cancerous tissue in the breast. However, the mature cells cannot be carried away as can those in the blood stream, so that when they grow old and die *in situ* there may occur necrosis, changes in the blood vessels, and, possibly, fibrosis. These cells, like those of the blood, have a latent period between the time of irradiation and the clinical response which corresponds to the time necessary for that particular type of cell to mature and to die of senility.

Of the stages in the development of the polymorphonuclear leukocyte, that of the myeloblast or primitive myeloblast is the only one in which the cell can divide and give rise to daughter cells. Cells in stages older than this are on the way to differentiation and never divide. Stimulation during the myeloblastic stage results in increased cell division. This is noted clinically in the exacerbation of symptoms after irradiation in leukemias in the acute (myeloblastic or lymphoblastic) stage. A similar division in growth potentialities is noted in the lymphoblastic and older stages of lymphocytes, erythroblasts and more mature red blood cells. The cells, then, respond by continuing their normal physiologic processes. The myeloblasts, lymphoblasts and erythroblasts divide, and the cells in the older stages continue on the way to maturity. These observations are used clinically in causing immature cells to mature as in chronic leukemia, or myeloblasts to divide, as in roentgen therapy in

agranulocytosis (granulocytopenia)<sup>12</sup> or induction of remissions in anemia by the same method.<sup>4</sup> Another aspect of the same phenomenon is the resistance to roentgen rays of cells that have a long adult life, such as muscle cells, cells in the fibrous tissue and nerve cells. In cells in this type of tissue maturity is not normally followed by immediate death under physiologic conditions, and maturity stimulated by roentgen rays is not followed by death from senility as quickly as in cells in other tissues, such as leukocytes, germ cells and other cells that normally die shortly after maturity is reached. The muscle, fibrous tissue or nerve cells are, then, not more "resistant" to roentgen irradiation, they merely have a longer adult life and so appear to survive longer after radiation has been applied.

#### SUMMARY AND CONCLUSIONS

The effect of roentgen irradiation, in both small and large doses, on developing blood cells is stimulating, the result depending on the stage of development of the cells. Cells in the myeloblastic, lymphoblastic or a younger stage are stimulated to rapid reproduction, because such is their growth potentiality at that stage, whereas cells in the myelocytic stage or the medium-sized lymphocytic stage are stimulated to grow through the rest of their life history in an orderly manner, because normally these cells do not divide and multiply. They die or are eliminated as normal, senile cells. There is no evidence of a toxic necrotic action of the roentgen rays when applied in therapeutic doses. The process is hastened by larger doses, so that senility is reached more quickly, giving the impression of a "depressing" action. The period between the application of the roentgen rays and the time when the cells reach senility is the latent period. This corresponds to the time necessary for the cells to mature. The action of roentgen rays on living, blood-forming cells is one of stimulation to divide or to mature in a normal manner and not one of toxic necrosis. Tissue cells which have a long adult life (muscle cells, nerve cells and fibrous tissue cells) appear resistant to roentgen rays, whereas those that have a short adult life (germ cells and leukocytes) die soon after they are "stimulated" to develop to senility. They all have the same susceptibility, but death follows at varying intervals, depending on how long the cells normally survive in their physiologic life.

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<sup>12</sup> Friedmann, U, and Elkeles, A. Die Rontgenbehandlung der Agranulozytose, *Deutsche med Wchnschr* **56** 947, 1930. Gager, L. T., and Speer, A. J. The Roentgen Treatment of Agranulocytosis, Report of Two Cases with Recovery. *Am J Roentgenol* **27** 40, 1932.

# ENDEMIC NUTRITIONAL EDEMA

## CLINICAL FINDINGS AND DIETARY STUDIES

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The association of edema and starvation, particularly in epidemics, has been recognized for centuries. The commoner causes of the under-nutrition are reflected in the terms "famine edema," "war edema," "prison edema," etc., which have been applied to this condition. During the World War edema attracted a great deal of attention, especially in Germany and the Central Powers where the reduction in food supplies made it extremely common. Still more recently it has been studied and reported among the population of certain famine districts in China.<sup>1</sup> The German studies, especially those of Schittenhelm and Schlecht,<sup>2</sup> Jansen,<sup>3</sup> Schittenhelm<sup>4</sup> and Knack and Neumann,<sup>5</sup> are of special interest since it was shown that this type of edema was associated with a hypoproteinemia, owing presumably to an insufficient supply of protein in the diet. Since then other studies have shown that cases not only of war edema but of other types of nutritional edema (Govaerts,<sup>6</sup> Peters, Bulger and

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1 (a) Ling, S. M. Change of Serum Proteins in Under-Nutrition, *Chinese J. Physiol.* **5** 1, 1931. (b) Weech, A. A., and Ling, S. M. Nutritional Edema. Observations on the Relation of the Serum Proteins to the Occurrence of Edema and to the Effect of Certain Inorganic Salts, *J. Clin. Investigation* **10** 869, 1931.

2 Schittenhelm, A., and Schlecht, H. Über die Odemkrankheit, *Ztschr. f. d. ges. exper. Med.* **9** 1, 1919.

3 Jansen, W. H. Die Odemkrankheit. Studien über die Physiologie der Unterernährung und über die Odempathogenese, *Deutsches Arch. f. klin. Med.* **144** 131 and 330, 1920.

4 Schittenhelm, A. Odemkrankheit in *Enzyklopaedie der klinische Medizin*, Berlin, Julius Springer, 1927, vol. 7, p. 738.

5 Knack, A. V., and Neumann, J. Beitrag zur Oedemfrage, *Deutsche med. Wchnschr.* **43** 901, 1917.

6 Govaerts, P. Recherches cliniques sur le rôle de la pression osmotique des protéines du sang dans la pathogénie des oedemes et de l'hypertension artérielle. *Bull. Acad. roy. d. méd. de Belgique* **4** 161, 1924.

Eisenman,<sup>7</sup> Peters, Wakeman and Eisenman,<sup>8</sup> and Weech and Ling<sup>1b</sup> are associated with a decrease in the plasma proteins, affecting mainly the albumin fraction. This finding, in the light of Starling's<sup>9</sup> hypothesis, has suggested that the reduction in plasma proteins plays an important rôle in the production of this type of edema.<sup>10</sup> Kohman<sup>11</sup> has produced an edema experimentally in rats by feeding a diet low in protein. Frisch, Mendel and Peters<sup>12</sup> have confirmed Kohman's results and in addition have shown that such protein-poor diets cause a deficiency in the plasma proteins. It has been shown that the edema of nephrosis<sup>13</sup> and of chronic nephritis<sup>14</sup> is closely related to a reduction in plasma proteins, owing, in part at least, to a loss of protein in the urine, and possibly in part to a protein starvation.<sup>14c</sup> The experimental production of edema in dogs by the process of plasmapheresis (Leiter,<sup>15</sup> Barker and Kirk,<sup>16</sup> Shelburne and Egloff<sup>17</sup>) further emphasizes the importance of plasma proteins in relation to edema. So close, in fact, is this relationship that

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7 Peters, J. P., Bulger, H. A., and Eisenman, A. J. The Plasma Proteins in Relation to Blood Hydration. II In Diabetes Mellitus, *J. Clin. Investigation* **1** 451, 1925

8 Peters, J. P., Wakeman, A. M., and Eisenman, A. J. The Plasma Proteins in Relation to Blood Hydration. III The Plasma Proteins in Malnutrition, *J. Clin. Investigation* **3** 491, 1927

9 Starling, E. H. On the Absorption of Fluids from the Connective Tissue Spaces, *J. Physiol.* **19** 312, 1895-1896

10 Weech and Ling<sup>1b</sup> Schuttenhelm and Schlecht<sup>2</sup> Bruckman, F. S., D'Esopo, L. M., and Peters, J. P. The Plasma Proteins in Relation to Blood Hydration. IV Malnutrition and the Serum Proteins, *J. Clin. Investigation* **8** 577, 1930

11 Kohman, E. A. The Experimental Production of Edema as Related to Protein Deficiency, *Am. J. Physiol.* **51** 378, 1920

12 Frisch, R. A., Mendel, L. B., and Peters, J. P. The Production of Edema and Serum Protein Deficiency in White Rats by Low Protein Diet, *J. Biol. Chem.* **84** 167, 1929

13 Epstein, A. A. Further Observations on the Nature and Treatment of Chronic Nephrosis, *Am. J. M. Sc.* **163** 167, 1922

14 (a) Linder, G. C., Lundsgaard, C., and Van Slyke, D. D. The Concentration of the Plasma Proteins in Nephritis, *J. Exper. Med.* **39** 887, 1924. (b) Moore, N. S., and Van Slyke, D. D. The Relationship Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, *J. Clin. Investigation* **8** 337, 1930. (c) Peters, J. P., Bruckman, F. S., Eisenman, A. J., Held, P. N., and Wakeman, A. M. The Plasma Proteins in Relation to Blood Hydration. VI Serum Proteins in Nephritic Edema, *J. Clin. Investigation* **10** 941, 1931

15 Leiter, L. Experimental Nephritic Edema, *Arch. Int. Med.* **48** 1 (July) 1931

16 Barker, M. H., and Kirk, E. J. Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, *Arch. Int. Med.* **45** 319 (March) 1930

17 Shelburne, S. A., and Egloff, W. C. Experimental Edema, *Arch. Int. Med.* **48** 51, 1931

various critical levels of serum albumin, below which edema is almost always present and above which it is usually absent, have been described in different types of edema<sup>18</sup>

In the last few years a number of cases of nutritional edema with lowered serum protein have been reported in this country<sup>19</sup> These have been sporadic cases, in most of which the edema accompanied some disease, such as tuberculosis, diabetes, cancer or gastro-intestinal disorders, which was responsible for an insufficient intake or an inadequate absorption or utilization of food In infants a similar sporadic edema occurs as a result of improper diet, or in association with various diseases<sup>20</sup> The existence of uncomplicated epidemic or endemic nutritional edema has scarcely been suspected

During the spring and summer of 1929, our attention was first attracted to a number of patients with an obscure edema They complained of swelling, usually of the feet and legs but sometimes of the face and hands as well Many of them gave a history of previous attacks Besides the edema, many complained of pain and tenderness in the legs and of indefinite pains in the joints Although a few had incidental conditions not related to the edema, the swelling was the only complaint in the great majority Most of the patients were women Examination showed a soft pitting edema, but investigation failed to reveal any of the usual causes It was first thought that the edema was due to a mild heart failure, but the cardiovascular findings were insufficient to explain it The urine and renal functional tests were normal Most of the patients were somewhat anemic, but with the possible exception of one case the anemia was not severe enough to cause the edema, and some of the patients had no anemia The idea that these might be cases of nutritional edema suggested itself, though there was no obvious cause for a widespread undernutrition and the economic situation at that time was generally satisfactory It was known, however, that the customary diet of a large part of the population of this part of Tennessee was of a character which might result in a low protein intake, consisting as it did in the main of highly milled cereals, fats, cooked leafy vegetables and relatively little animal protein Therefore the total serum protein was determined in several instances It was found to be normal or higher than normal Before arrangements for a more complete study could be made, it was late summer, no new cases appeared and

18 Weech and Ling<sup>1b</sup> Moore and Van Slyke<sup>14b</sup> Peters et al<sup>14c</sup>

19 Peters, Bulger and Eisenman<sup>7</sup> Peters, Wakeman and Eisenman<sup>8</sup> Landis, E M, and Leopold, S S Inanition Edema Associated with Tuberculous Enteritis, *J A M A* **94** 1378, 1930 Wolferth, C C Inanition Edema Associated with Alimentary Disturbance in Adults, *M Clin North America* **8** 785, 1924

20 Unpublished observations, Department of Pediatrics, Vanderbilt University Hospital



the old patients lost their edema. However, similar cases have appeared each year since, until a total of more than fifty have been observed. They are most often first seen in the late winter and spring, and increase in number through the spring and early summer. Toward fall new cases fail to appear, and the old patients lose their edema. It is the purpose of this paper to present the clinical findings in thirty-one of these patients who were studied fairly completely, together with a study of the diet of twelve of them. The results of a study of the serum proteins and of the nitrogen balance are reported in the succeeding paper.

#### MATERIAL AND METHODS

With two exceptions, all the patients were studied and followed in the outpatient department. In addition to the usual history and physical examination, the study included, in most of the cases, repeated urinalysis, the usual estimation of erythrocytes, leukocytes and hemoglobin and study of a stained smear, the Wassermann and phenolsulphonphthalein renal functional tests, an orthodiagram of the chest, an electrocardiogram, determination of the nonprotein nitrogen of the blood and a determination of the basal metabolic rate. A gastric analysis, examination of the stool and a reticulocyte count were made in a number of instances. In a few of the earlier cases the presence of edema was checked by the salt solution absorption test (McClure and Aldrich<sup>21</sup>). The serum proteins were determined at the time of the first visit or within a few days thereafter. The various laboratory examinations were made according to the usual standard methods. Nonprotein nitrogen was determined according to the method of Folin<sup>22</sup>. The basal metabolic rate was determined with a Roth-Benedict apparatus. In a number of the later cases the hemoglobin was determined with a calibrated Sahli instrument and the values expressed in grams of hemoglobin per hundred cubic centimeters, but for convenience all values are expressed in Sahli units. In those cases in which an achlorhydria was found with a simple test meal the examination was repeated after the injection of histamine.

The diet of twelve of the patients was ascertained before the institution of treatment or experimental procedures by having the patient keep an accurate record of the food eaten for a number of days. Printed slips were provided on which the amounts and kind of food taken each day were recorded. The procedure was carefully explained to the patient, not only by the physician but also by a social worker who sometimes visited the patient at home during this period to assist in keeping the record and to check its accuracy. From this record the total calories, and the total protein, animal protein, fat and carbohydrates were calculated.<sup>23</sup>

#### RESULTS

The principal clinical data are summarized in table 1 and may be presented briefly as follows. The ages of the patients varied from 20

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21 McClure, W. B., and Aldrich, C. A. Time Required for the Disappearance of Intradermally Injected Salt Solution. Preliminary Report of Observations, with Special Reference to Cases of Edema, *J. A. M. A.* **81** 293, 1923.

22 Folin, O. Laboratory Manual of Biological Chemistry with Supplement, ed. 4, New York, D. Appleton and Company, 1925.

23 Mrs. Stow and Miss Winckler, Directors of Dietetics of the Vanderbilt University Hospital, performed these calculations.

to 76, the majority being between 30 and 60. Eighteen were colored and thirteen were white. There were twenty-six women and five men. The duration of the edema varied from two days to a period of several years. It had been present a week or less in seven, from one to four weeks in seven, for several months in eight and for a year or more in five. In the latter the disease had been present intermittently. The duration was unknown in four cases. Edema of either the feet or the legs alone, or of the two together, occurred in twenty-one. In nine there was swelling of the face, hands or both, in addition to the swelling of the feet and legs. In one case the face alone was swollen. Fourteen patients gave a history of previous similar attacks and in two there was a history of swelling of the face and hands which was not present at the time they were observed. The amount of edema has been recorded as follows: slight but definite pitting edema of the feet and lower one third of the leg, +, moderate pitting edema of the same regions, ++, pitting edema of the feet and lower two thirds of the leg, +++, and pitting edema up to the knees, ++++. The quantitative measure of edema is of course unsatisfactory, owing in part to the well known difficulties in estimating the degree of edema and in part to diurnal and other variations in the edema which will be discussed. The degree of edema was + in sixteen, ++ in six, +++ in five and ++++ in two. The edema was questionable or absent at the time of examination in two. In several cases the edema was greater than the maximum indicated by this system of grading.

The heart was entirely normal in twenty-seven. As might be expected from the ages of some of the patients, a few showed some cardiac abnormalities, but in no case was there evidence of congestive failure other than edema. Three had a slight or questionable enlargement of the heart and only one showed as much as a moderate enlargement. The latter had occasional extrasystoles, and one (case 18) had a bundle branch block shown by electrocardiogram. The blood pressure was normal in nearly all, the systolic pressure being below 150 in all but two, with corresponding diastolic pressures. In case 18, with slight cardiac enlargement, the pressure was 180 systolic and 98 diastolic, in case 19, with moderate enlargement, 200 systolic, 110 diastolic. In one case the blood pressure was not determined.

A slight albuminuria was present in four, in one on a single occasion only. Casts were found only three times and an occasional red blood cell was found in uncatheterized specimens (women) twice. The phenol-sulphonphthalein excretion was above 50 per cent in the twenty-three in whom the test was done, and above 60 per cent in nineteen. The non-protein nitrogen of the blood was within normal limits in every case.

TABLE 1—Summary of Clinical Data in Thirty-One Patients with Edema

Case, Sex, Patient	Date	Age	Height, Cm	Weight, Kg	Edema			Kidney				Blood			Free Hydrochloric Acid	Basal Metabolic Rate, per Cent	Salt Solution Absorption Time, Min
					Duration	Location	Previous Attacks	Blood Pressure, Mm Hg	Albumin and Casts	Cells	Phenol sulphophthalein, per Cent	Hemo globin, per Cent	Red Cells, Mil	Nonprotein Nitrogen, Mg per 100 Cc	Wasser mann Test		
1, ♀ M T	6/18/29	35	170.2	73.1	+++	Feet, legs, hands	+	Normal	Albumin, 0 Casts, 0	0	75	52	390	24.0	Positive	0	— 8
2, ♀ M N	7/19/29	24	165.1	55.4	+	Intermittently	+	Normal	Albumin, 0 Casts, 0	Few white	75	68	324	24.0	Doubtful	+	40
3, ♀ W B	7/10/29	32	167.6	88.6	++	Feet, legs	+	Slightly enlarged (x-ray)	Albumin, 0 Casts, 0	Few white	65	40	323	23.0	Negative	+	13-19
4, ♀ C D	7/23/29	37	160.0	50.9	+	Feet, legs	+	Normal	Albumin, 0 Casts, 0	Occas	75	35	342	32.4	Positive	+	60
5, ♀ Q S	3/25/30	24	161.3	70.9	+	Hands, legs	0	Normal	Albumin, 0 Casts, 0	4.5 white	80	74	395	25.0	Negative	+	13-19
6, ♀ A P	4/12/30	33	172.7	51.1	++	Feet, legs	+	Slightly enlarged	Albumin, 0 Casts, 0	5 white	92	60	415	20.0	Negative	+	2
7, ♀ L A	4/30/30	42	163.8	76.8	+	Feet, legs	0	Normal	Albumin, 0 Casts, 0	Many white	65	70	126	27.2	Negative	+	45
8, ♂ J L	7/15/30	45	167.6	52.4	++	Feet, legs	0	Normal	Albumin, 0 Casts, 0	0		62	381	25.6	Negative		
9, ♀ M H	7/ 9/30	71	152.4	80.1	+++	Feet, legs	+	Normal	Albumin, 0 Casts, 0	0	50	60	530	26.8	Negative	+	1-12
10, ♀ J A	7/25/30	45	165.8	72.7	+	Feet, legs	0	Normal	Albumin, 0 Casts, 0	Red, white			307		Negative		
11, ♀ A D	7/30/30	50			+	Feet, legs	+	Normal	Albumin, 0 Casts, 0	Few white	70	85	424	30.7			1-15
12, ♀ W J	9/30/30	37	157.5	45.9	+	2½ months	0	Normal	Albumin, 0 Casts, 0	0	65	80	106	27.2	Negative		1
13, ♀ V H	11/19/30	50	165.1	50.9	+	Intermittently (years)	0	Normal	Albumin 0 Casts 0	Few white	60	68	371	31.5	Negative		Legs, 15 Arms, 20
14, ♀ M B	12/ 9/30	55	162.9	49.8	?	Feet	+	Normal	Albumin, 0 Casts, 0	0			25.0	Negative			1-10
15, ♀ I S	3/ 4/31	55	157.5	44.0	++	Feet, legs	?	Normal	Albumin, trace Casts 0	Occas white		64	401	31.5	Negative	+	

16, ♀ G R	3/ 9/31	30	166 1	81 5	++ +	3 months	Feet, legs	0	Normal	136/ 91	Albumin, trace Casts, 0	Occas white	70	78	4 29	26 6	Positive	+	+12
17, ♀ K V	1/18/31	48	160 7	46 3	++ + +	1 week	Feet, legs, face	0	Normal	135/ 80	Albumin, + later, 0 Casts, occas cellular and granular	Occas white	80	52	4 62	35 2	Negative	+	- 7
18, ♂ A C	1/20/31	62	170 2	62 6	+	10 days	Ankles	0	Bundle branch block, slight enlargement to left	180/ 98	Albumin, 0 Casts, few (hyaline)	Many white	50	65	4 28	31 5	Negative		
19, ♂ S M	1/ 6/31	76	172 7	61 3	++ + +	4 weeks	Feet, legs	+	Moderate enlargement, occasional extrastotic	200/110	Albumin, 0 Casts, 0	0	65	80	4 95	24 4	Positive		
20, ♂ J N *	1/23/31	60	172 7	65 1	++ +	1 week	Feet, legs	+	Normal	106/ 60	Albumin, 0 Casts, occas hyaline and granular	Few white	55	83	3 79	30 7	Negative	+	(1928)
21, ♀ S C	1/13/31	59	151 9	51 5	+	Intermit tently over 1 year	1 yes, feet, legs	+	Normal	124/ 70	Albumin, 0 Casts, 0	0	75			31 5	Negative		+21
22, ♂ J R	1/28/31	20	181 2	81 7	++ +	3 days	Face, hands, feet, legs	0	Normal	118/ 76	Albumin, 0 Casts, 0	Occas white	70	59	3 91	27 0	Negative	+	
23, ♀ J W	5/27/31	52	156 2	59 0	0	2 weeks	Feet, legs, hands (?)	0	Normal	110/ 50	Albumin, 0 Casts, 0	10-15 white				25 0	Negative		
24, ♀ E II	6/ 6/31	27	168 3	50 9	+	?	Legs	0	Normal	100/ 60	Albumin, 0 Casts, 0	Occas white	55	56	3 98	25 0	Negative		
27, ♀ A W	6/23/31	49	180 3	90 9	+	3 months	Face, legs	+	Normal including hands	110/ 88	Albumin, 0 Casts, 0	0	90	76	4 53	29 5	Negative	+	
26, ♀ L R	6/23/31	41	102 7		+	1 week	Feet, legs	+	also Normal face, hands		Albumin 0 Casts, 0	0		85	4 65	26 0	Negative		+ 9
27, ♀ M R	7/ 7/31	40	162 6	73 6	±	4 5 months	Legs	0	Normal	116/ 82	Albumin, 0 Casts, 0	6-8 white	70	69	3 86	26 0	Negative	+	- 9
28, ♀ K S	7/ 8/31	29	151 9	50 6	+	1 week	Feet, legs, face	+	Normal	126/ 78	Albumin, 0 Casts, 0	0		63	3 78	35 0	Negative		
29, ♀ B V	7/ 3/31	32	160 0	88 6	+	Several weeks	Feet, legs	0	Normal	110/ 68	Albumin, 0 Casts, 0	2-4 white	82	71	3 90	22 6	Negative	+	
30, ♀ M R	7/27/31	52	170 2	67 5	++ +	3 weeks	Feet, legs, face	0	Normal	148/100	Albumin, 0 Casts, 0	0				32 1	Negative		
31, ♀ L D	7/29/31	40	151 9	39 8	+	6 weeks	Face	0	Normal	104/ 62	Albumin, 0 Casts, 0	0	60	83	4 70	26 6	Negative		

\* Treated previously for pellagra ♂ indicates male, ♀, female

A secondary anemia of slight or moderate severity was found in nearly all the patients. The red cells were above 3 000,000 in all that were examined. The hemoglobin ranged from 40 to 85 per cent (Sahli). The color index was over 1 in but a single case. In the few cases in which counts were made, the reticulocytes were found to be very few.

The Wassermann reaction was positive in four, doubtful in one and not obtained in one. In none was there clinical evidence of active syphilis.

A gastric analysis was done in fifteen cases. Free hydrochloric acid was present in normal amounts in twelve, and hypo-acidity in one, in two there was achlorhydria even after an injection of histamine. The stools were examined in twelve cases. One showed mucus, meat fibers and flagellates. In one case *Trichuris*, *Endolimax nana* and a positive guaiac reaction were found on one occasion only, subsequent examinations gave negative results.

The basal metabolic rate was determined in seventeen of the patients. Values within the normal range ( $+01$  —  $10$ ) were found in all but four. The rate was  $+12$  in two, and  $+15$  and  $+24$  in one each. Single determinations were made in these four. Only one patient presented signs suggesting thyrotoxicosis.

In a few of the earlier cases the salt solution absorption test for edema was made. The absorption time varied from four to sixty minutes. In all but one the time was less than forty-five minutes.

Severe undernutrition was uncommon and practically no one was emaciated even after the loss of edema. Only sixteen were under their calculated ideal weight, while several of the thirteen who were overweight were actually obese. The weight was not recorded in two. No allowance has been made for the edema in these calculations, and it is probable that a number of these who were apparently slightly overweight were actually underweight. However, even those who were definitely overweight often gave a history of loss of weight preceding the appearance of the edema, and such losses were observed in patients as they were followed during periods of edema and of freedom from edema.

The average daily intake of protein, animal protein, carbohydrate and fat and the total calories in twelve cases are summarized in table 2. The calculated basal caloric requirement in each case is presented for comparison. Because of the relatively short periods, single days in which an exceptionally low intake was recorded have been omitted from these calculations in two cases (cases 7 and 29). In every instance but one the caloric value of the diet is seen to be below the calculated basal requirements. Since all were outpatients and more or less active, the deficiency is more striking. However though it is believed that the

records are fairly accurate, the total caloric intake was probably somewhat greater than is recorded. Considerable amounts of fat were used in cooking and have not been included in these calculations. The daily records showed considerable variation, and had the study been made over a longer period, it seems probable that a higher average would have been found. Nevertheless, the total caloric intake was undoubtedly very near the bare maintenance level in most instances. The average daily intake of protein was low, ranging from 20 to 52 Gm daily. In eight cases the protein intake was below the usually accepted minimum of from 0.5 to 0.7 Gm per kilogram,<sup>24</sup> and in the rest was below 1.0 Gm per kilogram. Animal protein amounted to from 41 to 70 per cent of the total protein. The rather high ratio of animal to total protein was at first surprising, but on reflection it was apparent that this finding

TABLE 2—Average Daily Food Intake Before the Institution of Treatment

Case	Weight	Calcu lated Basal Requirement, Calories	Intake							Number of Days
			Total Calories	Protein, Gm	per Kg, Gm	Animal Protein		Fat, Gm	Carbo hydrate, Gm	
						Gm	Per Cent			
5	69.8	1,554	790	31	0.44	18	58			6
7	76.8	1,590	390	26	0.33	15	57	38	101	6
9	80.4	1,551	907	31	0.38	15	48	41	111	6
13	50.9	1,294	1,106	45	0.88	31	69	46	127	6
16	81.5	1,664	1,396	41	0.41	18	44	76	137	6
17	46.3	1,253	887	31	0.66	17	55	31	121	4
18	63.6	1,524	1,012	38	0.59	23	61	50	104	4
19	61.3	1,517	515	20	0.32	12	60	26	48	5
21	54.5	1,302	1,377	52	0.95	34	65	79	114	3
27	73.6	1,555	1,018	33	0.44	18	55	33	148	5
28	50.6	1,305	854	22	0.43	9	41	34	112	6
29	88.6	1,638	1,140	44	0.49	31	70	38	123	6

might have been expected, since the usual diet contained so little total protein that any animal protein present must have made up the greater part of it.

#### COMMENT

These cases of edema differ in several respects from cases of nutritional edema previously reported, particularly those seen in epidemics. Clinically there is presented a mild edema, endemic in nature, with apparently a fairly high incidence among the part of the population from which these patients are drawn, and with a pronounced tendency to a seasonal (spring and summer) incidence. The edema was rarely as great as that reported among the starving populations during the war or more recently from famine districts in China.<sup>1</sup> Neither were the patients greatly undernourished. This absence of severe undernutrition also serves in part to distinguish these cases from those in which edema occurs in association with some disease which causes a severe under-

<sup>24</sup> Sherman, H. C. Protein Requirement of Maintenance in Man and the Nutrient Efficiency of Bread Protein, *J Biol Chem* **41** 97, 1920.

nutrition It should be emphasized that in the cases reported here such diseases were absent, and, except for occasional and incidental conditions not related to the edema, the latter was the principle complaint. It is this feature which particularly distinguishes them from the usual case of sporadic nutritional edema.

In comparing further these cases with those observed during the War, or more recently in China, there is noted a general absence of the bradycardia, hypotension, subnormal body temperatures and lowered metabolic rate frequently present in the latter. The tendency to tachycardia and shortness of breath on exertion, observed in cases of war edema, was noted occasionally. Unusual fatigue and loss of strength were infrequent. In both groups the heart and kidneys were essentially normal. In the present study no information was obtained regarding polyuria, which was a rather prominent feature in cases of war edema. A secondary anemia was apparently more frequent in our series, and there were no cleancut cases of blood concentration with a high red cell count and hemoglobin content, such as were observed by Schittenhelm and Schlecht<sup>2</sup> and by Jansen<sup>3</sup>. All these observations are consistent with the mild nature of the disease and the absence of severe general undernutrition.

The mild nature of the disease is explained by the absence of a severe and relatively acute deprivation of food. In spite of the apparently great reduction in food intake, as shown in table 2, there is reason to believe that the dietary deficiency is principally a protein shortage, with the total caloric intake near the minimal requirements. On the other hand, this dietary deficiency had probably existed for years. The dietary studies were made at the time of the appearance of edema, when there might well have been a temporary reduction in food intake sufficient to produce symptoms in a person whose diet was ordinarily barely sufficient. The periods are too short to permit the assumption that the caloric intake represented the average over a long period of time. Furthermore, the diet is more a matter of custom and habit than of necessity. This conception of the nature of the dietary insufficiency is supported by the fact that few of the patients were greatly underweight and at least half were of normal weight or above, though even the latter often gave a history of loss of weight some time before the onset of the edema. To some extent at least, the absence of a greater edema may be due to the relatively low water content of the diet as compared with the diet in the cases of war edema.

The insufficiency of protein is clearly shown by these studies even though allowance is made for the fact that the amounts may have been somewhat greater at some periods. In general, the values are less than those given by Jansen<sup>3</sup> in his cases of war edema (group A), and in

most instances are well below the usual minimum requirements. They are more significant in view of the low caloric intake, since it is known that though nitrogen equilibrium may be maintained in a protein intake as low as recorded here, it is necessary that the total calories be high. In addition, no allowance has been made for the loss of nitrogen in the stool, which may have been greater than usual on a diet of this type, or for the availability of some of the types of protein in the diet. On the other hand, interference with absorption due to diarrhea or other disease of the gastro-intestinal tract was apparently not a factor. Further evidence of protein starvation is obtained from the studies of nitrogen balance reported in the succeeding paper.

The possibility that the edema in these cases is present as a part of some specific deficiency disease (avitaminosis) must be considered. The same question was raised in connection with the cases during the War and particularly in connection with similar cases of edema disease seen in India<sup>25</sup>. A mild or abortive form of beriberi seems to be the only recognized disease compatible with the findings which these patients present. Aside from the edema, the only feature which suggests beriberi is the occurrence of mild pain in the extremities and tenderness over the affected areas. This tenderness occurs in other forms of edema, however, and while it is impossible to prove that these are not mild cases of beriberi, the absence of more definite peripheral nerve changes, the presence of normal reflexes and the lack of fully developed and characteristic cases among so many mild ones makes beriberi unlikely.

The greater frequency at certain seasons is difficult to explain. A preliminary inquiry into the dietary habits of the patients did not reveal any particular difference between the summer and winter months. It might be that during the colder weather the greater caloric requirements lead to a relatively greater food deficiency which finds expression in the occurrence of edema some time later. Nutritional edema is particularly affected by variations in the fluid intake, and it is possible that the greater incidence in warmer weather is related to a larger intake of water at that time. An increase in venous pressure during warm weather may favor the formation of edema, but it is difficult to reconcile this with the tendency for the edema to disappear in the late summer.

The amount of edema varied considerably from time to time, a finding which has been observed by others. These changes occurred with considerable rapidity, and a well marked edema might disappear almost entirely in a day or so, only to reappear again. These changes occurred not only in association with such well known factors as rest and activity (diurnal and nocturnal variations), but in the absence of any known

<sup>25</sup> Ray, C. Epidemic Dropsy. Its Blood Picture, General and Biochemical, Indian J. M. Research **15** 67, 1927.



cause and often without any relation to treatment. Similar changes in the edema without change in the serum protein were observed by Moore and Van Slyke<sup>14b</sup> in cases of chronic nephritis and by Shelburne and Egloff<sup>17</sup> in dogs made edematous by plasmapheresis.

#### SUMMARY

The clinical findings in a group of patients whose principal complaint was a mild edema, apparently nutritional in nature, are reported. The diet of twelve of these patients was determined before the institution of treatment or experimental studies. In all but one the total calories were below the basal requirements. The average protein intake ranged from 20 to 52 Gm daily, and was below the usual minimum (from 0.5 to 0.7 Gm per kilogram) in all but four cases. It is believed that these patients were suffering from a chronic dietary deficiency, particularly a shortage of protein, with an accompanying nutritional edema.

# DIFFUSIBLE CALCIUM OF THE BLOOD STREAM

## V INFLUENCE OF AGENTS WHICH AFFECT BLOOD CALCIUM ON CALCIUM DISTRIBUTION AND INORGANIC PHOSPHATE OF THE SERUM

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The use of agents capable of influencing the calcium content of the blood in the treatment of many pathologic conditions has become a widespread medical procedure<sup>1</sup> When there is any rational basis at all, the purpose of these reagents is to counteract a deficiency, presumed or real, in blood or tissue calcium In some instances, it is true, the treatment is given, not for the direct effect on calcium, but for secondary effects such as to decrease hemorrhagic tendencies or to relieve edema A sound rational basis for calcium therapy depends on an extensive knowledge of the influence of the agents commonly employed on the biochemistry of the body calcium and other bodily constituents that are interrelated with the calcium Since it is naturally difficult to study the whole of the body calcium, attention has been given mainly to the effect on the blood calcium Many studies have been devoted in years past to agents capable of influencing the level of blood calcium In the main, these agents consist of calcium-containing compounds, extracts of the parathyroid gland, irradiation with ultraviolet light and various preparations of the antirachitic vitamin D The bulk of these studies has been confined to the measurement of the changes produced in the total serum calcium alone

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Eli Lilly & Co furnished the parathyroid extract-Collip used in the experiments

Presented at a meeting of the American Association for the Advancement of Science, Pasadena, Calif, June 16, 1931

From the Division of Biochemistry and the Department of Medicine, University of California Medical School, Berkeley and San Francisco

1 (a) Peters, J P, and Van Slyke, D D Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, chap 16 (b) Herzfeld, E, Lubowski, H, and Kruger, R Die klinische Bedeutung des Serumkalkspiegels beim Menschen, Kritische Uebersicht (1923-1928), Folia haemat **41** 73 (May) 1930 (c) Cantarow, A Calcium Metabolism and Calcium Therapy, Philadelphia, P Blakiston's Son & Co, 1931

As a result of the many studies on the biochemistry of blood calcium, it is generally accepted that the calcium is present only in the plasma, and in the plasma it exists in at least two distinct fractions, commonly termed diffusible and nondiffusible calcium. These two fractions are distinguishable by the ability of the diffusible calcium to pass through a colloid impermeable membrane while the nondiffusible calcium is held back by such a membrane. It is now also widely held that the diffusible calcium is physiologically active while the nondiffusible calcium is apparently physiologically inert. Also, to add to the complexity, it has been suggested that there exists a functional relationship between the calcium, the proteins and the inorganic phosphate of the blood serum.<sup>2</sup> It is readily seen, then, that the study of the changes in the total calcium is not sufficient for a complete description of the action of substances influencing the level of the blood calcium. Since, as far as we were aware, no complete determination of the effect of agents capable of influencing the blood calcium had been carried out on the diffusible calcium, nondiffusible calcium and inorganic phosphate concurrently, such a series of experiments was undertaken by us. Sweet milk, acidified milk, a number of calcium salts and parathyroid extract were used as test substances in the experiments.

The purpose of these studies was not only to accumulate data which would be serviceable in securing a fundamental basis for calcium therapy, but also to obtain by these experiments a deeper insight into the postulated relationships between diffusible calcium, nondiffusible calcium proteins and inorganic phosphate.

When a closer consideration is given to the factors underlying the connection between these quantities, it becomes probable, in the light of present-day knowledge, that in the first instance the relationship of the phosphate level is with the diffusible calcium, while that of the protein is with the nondiffusible fraction. Any connection between inorganic serum phosphate and calcium would be logically expected to spring from the rôle of these two ions in the mechanism of calcification, a subject which has been extensively studied *in vitro* by Shipley, Kramer and

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2 (a) Loeb, R. F., and Nichols, E. G. Factors Influencing the Diffusibility of Calcium in Human Blood Serum, *J. Biol. Chem.* **72** 687 (April) 1927. (b) Greenberg, D. M., and Gunther, L. On Determination of Diffusible and Non-Diffusible Serum Calcium, *ibid.* **85** 491 (Jan.) 1930. (c) Salvesen, H. A., and Linder, G. C. Inorganic Bases and Phosphates in Relation to Protein of Blood and Other Body Fluids in Bright's Disease and in Heart Failure, *ibid.* **58** 617 and 635 (Dec.) 1923. (d) Howland, J., and Kramer, B. Factors Concerned in the Calcification of Bone, *Tr. Am. Pediat. Soc.* **34** 204, 1922. (e) Peters, J. P., and Eiserich, L. Influence of Protein and Inorganic Phosphorus on Serum Calcium, *J. Biol. Chem.* **84** 155 (Oct.) 1929.

Howland,<sup>3</sup> Robison,<sup>4</sup> Holt, La Mer and Chown,<sup>5</sup> Sendroy and Hastings,<sup>6</sup> Shear and Kramer<sup>7</sup> and many others. The basic idea of all these studies is that calcification is dependent on the solubility product of some sparingly soluble calcium and phosphate containing salt. If the solubility product of such a salt also governs the level of the calcium and phosphate ion in the blood stream, it is readily seen that the calcium content should vary inversely as the inorganic phosphate of the serum. Since it is the calcium ion which is involved in this relationship, and since in the blood it is the diffusible fraction which contains the calcium ion, it follows that the relationship which exists between the blood phosphate and calcium is primarily concerned with the diffusible calcium.

It should be noted that the inverse relationship postulated between calcium and inorganic phosphate is not always borne out, as is shown by the analytic results of Stearns and Knowlton<sup>8</sup> on the blood of children.

Reasoning in a similar way, since it is held that the nondiffusible calcium is combined in a nonionic way with the serum proteins,<sup>9</sup> the level of the proteins primarily affects the nondiffusible calcium. However, it has been pointed out by us<sup>2b</sup> that the diffusible calcium and nondiffusible calcium are not independent of each other, according to the results of experiments *in vitro*. Instead, when the protein and  $p_{H}$  are kept constant, the level of the nondiffusible calcium varies directly with the content of diffusible calcium. In this way, all four quantities have an influence on each other. By the use of agents influencing blood calcium and thus obtaining values far out of the ordinary range, the relationships that obtain between diffusible calcium, nondiffusible calcium, inorganic phosphate and protein would be expected to be accentuated and thus made more readily interpretable. Furthermore, such

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3 Shipley, P. G., Kramer, B., and Howland, J. Calcification *in Vitro*, *Biochem J* **20** 379, 1926

4 Robison, R. Possible Significance of Hexosephosphoric Esters in Ossification, *Biochem J* **17** 286, 1923

5 Holt, L. E., La Mer, V. K., and Chown, H. B. Studies in Calcification Solubility Product of Secondary and Tertiary Calcium Phosphate Under Various Conditions, *J Biol Chem* **64**, 509 and 576 (July) 1925

6 Sendroy, J., and Hastings, A. B. Studies on Solubility of Calcium Salts, *J Biol Chem* **71** 783 and 797 (Feb.) 1927

7 Shear, M. J., and Kramer, B. Composition of Bone. Equilibration of Serum with Dicalcium Phosphate, *J Biol Chem* **86** 677 (April) 1930

8 Stearns, G., and Knowlton, G. C. Lack of Relationship Between Calcium, Protein, and Inorganic Phosphorus of Serum of Non-Nephritic Children, *J Biol Chem* **92** 639 (Aug.) 1931

9 Loeb<sup>2a</sup> Greenberg, D. M. Electrical Transference of Calcium in Blood Serum Protein Solutions, *J Biol Chem* **79** 177 (Sept.) 1928. Shear, M. J., and Offner, M. M. Composition of Bone. Binding of Calcium Ions by Serum, *ibid* **91** 291 (April) 1931

experiments have the value that they are performed *in vivo*, in the organism itself, and thus have a greater significance for the biochemistry of blood calcium than experiments *in vitro*

At this point it is well to consider some objections that have been raised against the methods employed in determining diffusible calcium. From time to time such objections have been raised in the literature. For the present, we shall confine ourselves to some recent statements on the subject, noting that these objections are not wholly new. Osnato, Killian, Garcia and Mattice,<sup>10</sup> in summarizing the work done by means of ultrafiltration and compensation dialysis, pointed out that a wide variation in values has been obtained, ranging from 39 to 75 per cent of the total calcium. On the same subject, Morgulis and Perley<sup>11</sup> stated "The situation is not much more encouraging when we consider the diffusible and non-diffusible fractions of the serum or plasma calcium, because the results of different investigators are so much at variance and the methods of fractionating the calcium, namely compensation dialysis and ultrafiltration are not above criticism from a theoretical point of view." Hunter<sup>12</sup> again brought up the criticism that the results of ultrafiltration may be affected by the time of filtration and the pressure employed.

In a recent publication, one of us (Dr Greenberg<sup>13</sup>) has experimentally shown that ultrafiltration of electrolytes partakes of the nature of a Donnan membrane distribution, which leads to the corollary that ultrafiltration and compensation dialysis are analogous in principle. Even so, it is our opinion that the ultrafiltration method is superior to compensation dialysis in the determination of diffusible calcium, since no artificial dialysis liquid employed is completely balanced against all the constituents of the serum. This defect plays no part in ultrafiltration. The time of filtration and the pressure employed actually are of minor importance, as has already been pointed out in a previous communication.<sup>2b</sup> The all-important requirement for obtaining correct results by ultrafiltration is the use of proper membranes, and the preparation and testing of such membranes have also been considered in the communication just mentioned.

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10 Osnato, M, Killian, J A, Garcia, T, and Mattice, M R. Comparative Chemical Studies of Blood and Spinal Fluid in Epilepsy, *Brain* **50** 581 (Oct) 1927

11 Morgulis, S, and Perley, A M. Studies on Cerebrospinal Fluid and Serum Calcium, with Special Reference to Parathyroid Hormone, *J Biol Chem* **88** 169 (Aug) 1930

12 Hunter, D. Critical Review Metabolism of Calcium and Phosphorus and Parathyroids in Health and Disease, *Quart J Med* **24** 393 (April) 1931

13 Greenberg, D M, and Greenberg, M. Ultrafiltration I Ultrafiltration of Electrolytes from Alkali Caseinate Solutions, *J Biol Chem* **94** 373 (Dec) 1931

In some instances, it is true, extremely astonishing and doubtful results have been published. As an illustration, we shall consider one such instance on which we had the opportunity to check. Emerson<sup>14</sup> reported extremely low values for the diffusible calcium of jaundiced dogs, values in some instances of less than 2 mg per hundred cubic centimeters of serum. He also reported a continuous increase and terminally high values for both the total and the diffusible calcium in dogs in which a bile fistula was produced by a cholecystonephrostomy. The published figures for the diffusible calcium in jaundice by us<sup>15</sup> and by Snell and Greene<sup>16</sup> throw grave doubt on Emerson's figures. Dr. Werner Schmidt and C. L. A. Schmidt permitted us to make a series of analyses on a dog in which a bile renal fistula had been produced. The

TABLE 1—*Calcium Distribution in a Dog in Which a Bile-Renal Fistula Was Produced*

Date	Diet	Total Calcium	Diffusible Calcium	Plasma Carbon Dioxide, % by Vol
Feb 15, 1929	Bile added	9.70	5.70	55.6
Feb 18, 1929	Bile added	9.60	5.60	58.3
Feb 26, 1929	Bile free since Feb 18, 1929	9.30	5.50	61.9
March 6, 1929	Bile free since Feb 18, 1929	10.20	5.10	55.3
March 11, 1929	Bile free since Feb 18, 1929	10.4	5.70	40.5
April 12, 1929	Cod liver oil added since March 11, 1929	10.1	5.80	41.2

results obtained are given in table 1, and, again contrary to Emerson's figures, show very little change on a bile-free diet during a period of forty-five days. We point this out to illustrate that the indiscriminate use of all the published data in criticism of a method is not justifiable.

The best answer to the criticisms and the best justification for the validity of the diffusible calcium determination are that a host of workers in widely separated laboratories have obtained consistent and concordant results by the methods that we have employed.<sup>17</sup>

14 Emerson, W. C. Distribution of Calcium in Jaundiced and Acholic Dogs, *J. Lab. & Clin. Med.* **14** 122 (Nov.) 1928.

15 Gunther, L., and Greenberg, D. M. Diffusible Calcium and the Proteins of the Blood Serum in Jaundice, *Arch. Int. Med.* **45** 983 (June) 1930.

16 Snell, A. M., and Greene, C. H. Calcium in Serum in Jaundice, *Am. J. Physiol.* **92** 630 (April) 1930.

17 Pincus, J. B., Peterson, H. A., and Kramer, B. Study by Means of Ultrafiltration of Condition of Several Inorganic Constituents of Blood Serum in Disease, *J. Biol. Chem.* **68** 601 (June) 1926. Liu, S. H. Comparative Study of Effects of Various Treatments on Calcium and Phosphorus Metabolism in Tetany,

## EXPERIMENTAL WORK

In the experimental work reported here, time curves have been obtained on the influence of the ingestion of sweet milk, acidified milk and a number of calcium salts and the effect of the injection of parathyroid extract on the total calcium, diffusible calcium, nondiffusible calcium and inorganic phosphate of the blood serum. The experimental methods used in the analyses have been described by us<sup>2b</sup>. The experiments were carried out on both human subjects and dogs. The human subjects were medical students of both sexes. Rather large dogs were selected for the work. Throughout, the dogs were fed on a diet of bread and meat, with the addition of an occasional small portion of cod liver oil. The last meal before an experiment was carried out was taken on the evening previous to the experimental period, during the course of the experiment no food was allowed, but water was permitted *ad libitum*. The data are given in the form of graphs from representative experimental results obtained for the particular experimental procedure.

*Effect of Short Periods of Fasting*—The calcium changes of the blood in animals and man over prolonged periods of starvation have been studied by a considerable number of authors, among whom may be mentioned Cavins,<sup>18</sup> Morgulis,<sup>19</sup> Morgulis and Perley,<sup>20</sup> Farquharson and Tibbetts<sup>21</sup> and Lennox, O'Connor and Bellinger.<sup>22</sup> The net result of the work on this subject is that in starvation the calcium and inorganic phosphate undergo little change until an advanced stage of inanition is reached. However, in the experiments cited, blood was drawn and analyses were carried out only at intervals of several days.

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J Clin Investigation **5** 259 and 277 (Feb.) 1928. Reed, C. I. On the State of Plasma Calcium in Parathyroidectomized Dogs, J Biol Chem **77** 547 (May) 1928. Greene, C. H., and Power, M. H. Distribution of Electrolytes Between Serum and in Vivo Dialysate, *ibid* **91** 183 (April) 1931. Brown, H., and Ramsdell, S. G. Blood Calcium Distribution in Anaphylaxis in Guinea Pig, J Exper Med **49** 705 (May) 1929. McCance, R. A., and Watchorn, E. Inorganic Constituents of Cerebrospinal Fluid. Calcium and Magnesium, Quart J Med **24** 371 (April) 1931.

18 Cavins, A. W. Effect of Fasting (and Refeeding) on Calcium and Inorganic Phosphorus in Blood Serums of Normal and Rachitic Cats, J Biol Chem **59** 237 (Feb.) 1924.

19 Morgulis, S. Chemical Changes in Blood During Fasting and Subsequent Re-Feeding. Inorganic Components, Am J Physiol **84** 350 (March) 1928.

20 Morgulis, S., and Perley, A. M. Changes in Serum Calcium of Cats During Fasting, Am J Physiol **89** 213 (June) 1929.

21 Farquharson, R. F., and Tibbetts, D. M. Studies of Calcium and Phosphorus Metabolism. On Temporary Fluctuations in Level of Calcium and Inorganic Phosphorus in Blood Serum of Normal Individuals, J Clin Investigation **10** 271 (June) 1931.

22 Lennox, W. G., O'Connor, M., and Bellinger, M. Chemical Changes in the Blood During Fasting in the Human Subject, Arch Int Med **38** 553 (Nov.) 1926.

or longer, and so do not rule out the possibility that a daily cycle of change may be present in the calcium fractions and phosphate, perhaps dependent on the daily rhythm of the activities and habits of the subject. Such a cycle of changes, if it existed, would have a considerable bearing on any experiments designed to determine the effects of agents influencing blood calcium. Accordingly, a series of determinations was carried out on human subjects and dogs undergoing short fasting periods to detect such daily changes if they exist.

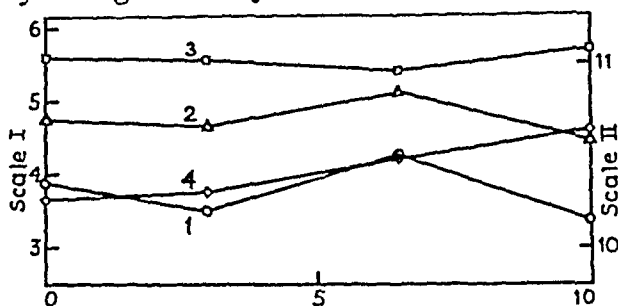


Chart 1—This experiment on a human subject (W) shows practically no fluctuation in calcium but a definite increase in inorganic serum phosphate of about 1 mm during a short period of fasting. In all of these charts (except chart 5) the magnitude of the total calcium is given by scale II on the ordinate on the right side of the drawing, while the amounts of diffusible calcium, nondiffusible calcium and inorganic serum phosphate are represented on scale I on the left side of the drawing. The abscissa measures the time in hours. In all cases, the curves for total calcium are numbered 1 and the experimental points are represented by the circles, the curves for diffusible calcium are numbered 2 and the points are shown by the triangles, curve 3 and the squares represent the nondiffusible calcium, the inorganic serum phosphate curves are numbered 4 and the experimental points are marked with the diamond-shaped symbols.

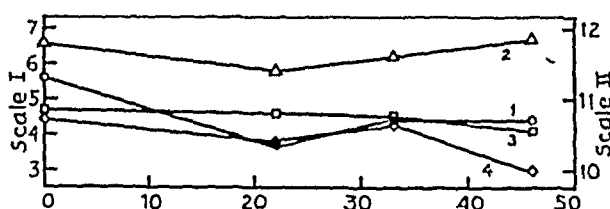


Chart 2—A short fasting period in a dog (dog 8, weighing 15 Kg) produces a small drop in calcium from the initial value with erratic changes in the inorganic serum phosphate.

In these experiments, food was last taken on the evening before the day of the experiment, the first sample of blood was drawn at about 8 a. m. the next day, and other samples of blood at varying intervals during the day. Curves, illustrating the kind of results obtained, are shown in chart 1 for a human subject, and in chart 2 for a dog. The curves, which are typical, show that there is a trend toward a small drop in the total calcium from the initial value. This small drop in the beginning may perhaps be taken to indicate that there ordinarily exists a



slight plethora of calcium which is brought down to a constant stable level soon after the start of the fasting period. This drop seems to be due to fluctuations in the diffusible calcium with almost no change in nondiffusible calcium. However, as the figures here are bordering on the limits of error of the analytic methods, a clearcut decision cannot be made. The changes of the inorganic phosphate during the fasting period were somewhat erratic, showing no well defined tendency.

These experiments rule out the possibility of daily rhythms taking place in the calcium and inorganic phosphate of sufficient magnitude to be important in obscuring the results of agencies that have an effect on blood calcium.

*Effect of Ingestion of Milk*—Milk is an important source of calcium for the whole of the animal kingdom. Furthermore, it has been shown that parathyroid-deficient animals fed on a milk diet can be kept free from tetanic symptoms.<sup>23</sup> Salvesen<sup>24</sup> has shown that this favorable influence of milk in parathyrioprivia is due to nothing else than its calcium content, calcium-free milk being ineffectual in this respect. From this, it readily follows that a study of the effect of the ingestion of milk on the calcium and phosphate content of the blood is of great interest, and accordingly was undertaken by us.

The experiments with milk were all carried out on human subjects. Without eating any breakfast, the subject drank 1 liter of milk at about 8 a. m. This amount of cow's milk contains about 1.2 Gm. of calcium and 0.93 Gm. of phosphorus.<sup>25</sup> A sample of blood to serve as a control was drawn immediately before the ingestion of milk and then further samples of blood were taken at varying intervals during the day. Two kinds of milk were employed in the experiment, pasteurized sweet milk and acidified milk prepared with lactic acid.<sup>26</sup>

Differences in the results were obtained with the two kinds of milk. With sweet milk there were no regular changes produced in serum calcium, while an increase took place in the inorganic phosphate, as is

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23 Dragstedt, L. R., and Peacock, S. C. Pathogenesis of Tetany. Control and Cure of Parathyroid Tetany by Diet, *Am. J. Physiol.* **64**: 424 (May) 1923.  
Inouye, T. Experimental Tetany and Diet, *ibid.* **70**: 524 (Nov.) 1924.

24 Salvesen, H. S. Studies on Physiology of Parathyroids, *Acta med. Scandinav.*, 1923-1924, supp. 6.

25 Sherman, H. C. *Chemistry of Food and Nutrition*, ed. 3, New York, The Macmillan Company, 1925, p. 590.

26 The acidified milk was prepared by the pediatrics department of the University of California Medical School according to the following formula. One hundred cubic centimeters of karo syrup is added to 1 liter of fresh milk, and the whole mixed thoroughly. The milk is then heated to boiling for three minutes and again cooled in an ice chest. When cold, 20 cc. of 85 per cent lactic acid is added, drop by drop, the milk being vigorously stirred during the procedure.

shown in chart 3. In some instances there were small increases (chart 3 *A*), and in others decreases (chart 3 *B*), of the total calcium amounting to several tenths of a milligram per hundred cubic centimeters. This was due to changes in the diffusible rather than the nondiffusible calcium. The changes in inorganic phosphate were not always constant, although most often there was an increase. The increase in the phosphate was about 1 mg per hundred cubic centimeters over a period of eight hours.

With acidified milk, on the contrary, a quite different picture was obtained. On this regimen, the calcium increased ordinarily by about 1 mg per hundred cubic centimeters, the whole of the increase again being in the diffusible fraction while the nondiffusible fraction remained constant, as is shown in chart 4. Along with the increase in the calcium there was an increase in inorganic phosphate, also to the value of about

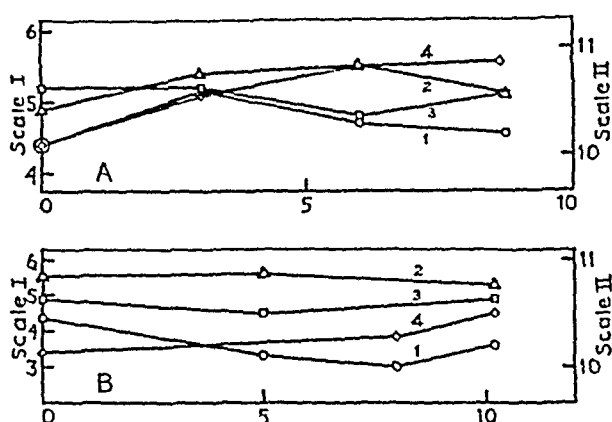


Chart 3—4, the effect of the ingestion of 1 liter of sweet milk (subject L), showing small erratic fluctuations in the calcium and an increase of about 1 mg per hundred cubic centimeters in the inorganic phosphate over an eight hour period. *B*, this experiment on the ingestion of sweet milk (subject S) shows a small drop in the calcium and, as in *A*, an increase in the phosphate.

1 mg per hundred cubic centimeters of serum. In both the calcium and the phosphate the maximum of the increase occurred about eight hours after the ingestion of the milk.

How is the difference in the behavior between the two types of milk to be explained? The explanation that seems plausible to us is that the height of the blood calcium after the ingestion of a calcium compound depends on a balance between absorption and the factors that make for the removal of calcium, such as excretion and deposition as bone and tissue calcium. On this reasoning, only when there is a marked excess of absorption is there a rise in the calcium level. Ordinary sweet milk does not favor a rapid absorption, since the balance between acid and basic radicals is such that a large part of the calcium is precipitated in the intestinal tract. On the other hand, acidified milk with its excessive acid content favors a greater content of soluble calcium.

in the intestinal tract, and other things being equal, this would favor absorption and tend to increase the level of blood calcium

*Effect of Ingestion of Calcium Salts*—The influence of ingested calcium salts on the blood calcium has been extensively investigated. Until only a few years ago, many of the workers on this subject reported that they were unable to increase the level of the blood calcium by the feeding of calcium salts. Among this group of authors were Meigs, Blatherwick and Carey,<sup>27</sup> Denis and Corley,<sup>28</sup> Halverson, Mohler and Bergeim,<sup>29</sup> Clark,<sup>30</sup> and Salvesen, Hastings and McIntosh.<sup>31</sup>

In the light of present-day knowledge it seems probable that this group of workers missed the increase in the blood calcium because of

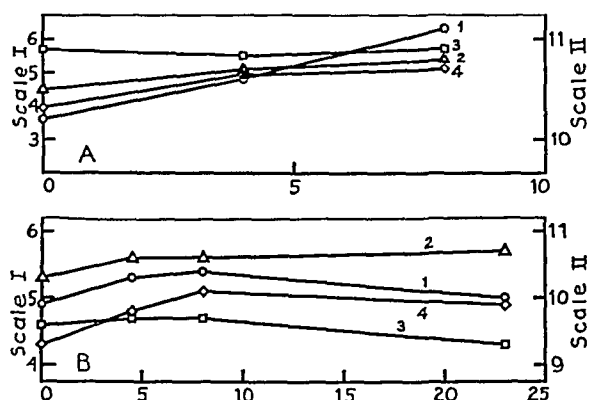


Chart 4—*A*, with the ingestion of 1 liter of acid milk (subject G), there is an increase of about 1 mg per hundred cubic centimeters in the serum calcium and also an increase in the inorganic phosphate as with sweet milk. It is to be noted that the increase in calcium is caused solely by an increase of the diffusible calcium. *B*, another experiment with acid milk (subject T), showing more definitely that the maximum of the calcium and phosphate increase comes about eight hours after ingestion of the milk.

shortcomings in the experimental procedure, the chief ones being failure to draw samples of blood at the right intervals and allowing the partaking of food during the experiments.

27 Meigs, E B, Blatherwick, N R, and Carey, C A. Contributions to the Physiology of Phosphorus and Calcium Metabolism as Related to Milk Secretion, *J Biol Chem* **37** 1 (Jan) 1919.

28 Denis, W, and Corley, R C. Study of Effect of Excessive Calcium Ingestion on the Calcium Content of Tissues With and Without the Application of Ultra-Violet Light, *J Biol Chem* **66** 609 (Dec) 1925.

29 Halverson, J O, Mohler, H H, and Bergeim, O. Calcium Content of Blood Serum in Certain Pathological Conditions, *J Biol Chem* **32** 171 (Nov) 1917.

30 Clark, G W. Effect of Hypodermic and Oral Administration of Calcium Salts on Calcium Content of Rabbit Blood, *J Biol Chem* **43** 89 (Aug) 1920.

31 Salvesen, H A, Hastings, A B, and McIntosh, J F. Effect of Administration of Calcium Salts on Inorganic Composition of Blood, *J Biol Chem* **60** 327 (June) 1924.

It has been conclusively shown that, when properly carried out, the ingestion of a soluble calcium salt produces an increase in blood calcium. The salts that have been most extensively employed have been calcium chloride, calcium lactate and, recently, calcium gluconate. From among the many studies may be cited those of Mason,<sup>32</sup> Blum, Aubel and Hausknecht,<sup>33</sup> Stewart and Haldane<sup>34</sup> and Lasch and Neumayer<sup>35</sup> on calcium chloride, those of Luckhardt and Goldberg<sup>36</sup> Kahn and Roe,<sup>37</sup>

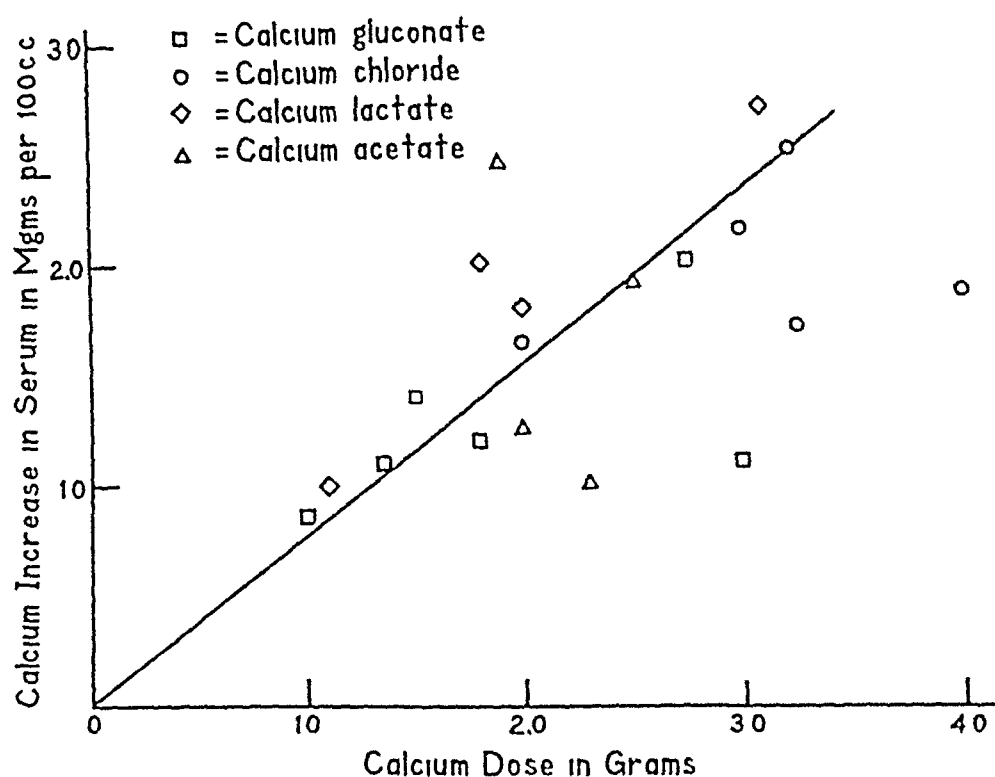


Chart 5—Plot of the increase in the serum calcium obtained in dogs after the oral ingestion of the salts listed in the drawing which indicates that the increase in calcium is proportional to the calcium content of the dose and is independent of the particular calcium salt employed

32 Mason, E. H. Absorption of Calcium Salts in Man, *J. Biol. Chem.* **47** 3 (June) 1921

33 Blum, L., Aubel, E., and Hausknecht, R. Modification de la composition minérale du sang et des humeurs après ingestion de chlorure de calcium, *Compt. rend. Soc. de biol.* **85** 1159, 1921

34 Stewart, C. P., and Haldane, J. B. S. Experimental Alterations in the Calcium Content of Human Serum and Urine, *Biochem. J.* **18** 855, 1924

35 Lasch, F., and Neumayer, K. Resorption of Calcium in Peroral Administration, *Biochem. Ztschr.* **174** 333, 1926

36 Luckhardt, A. B., and Goldberg, B. Preservation of the Life of Completely Parathyroidectomized Dogs, *J. A. M. A.* **80** 79 (Jan. 13) 1923

37 Kahn, B. S., and Roe, J. H. Calcium Absorption from the Intestinal Tract in Human Subjects, *J. A. M. A.* **86** 1761 (June 5) 1926

Bauer and Ropes<sup>38</sup> and Hoyle<sup>39</sup> on calcium lactate, those of Rothlin<sup>40</sup> and Liebermann<sup>41</sup> on calcium gluconate and those of Jansen<sup>42</sup> and Hjort<sup>43</sup> on a number of calcium salts

The most extensive series of such experiments is that of Hjort. The typical results according to his findings are: If the salt is administered on an empty stomach and in sufficient dosage, there is an increase in the serum calcium which reaches a maximum in about two hours and then drops back to the preingestion level in about four hours. This sequence of events is in agreement with the experience of most of the authors mentioned.

The amount of the increase obtained is a matter of some dispute. Kahn and Roe<sup>37</sup> claimed an elevation of 80 per cent in human subjects given 20 Gm of calcium lactate. Bauer and Ropes<sup>38</sup> took exception to Kahn and Roe's figure and stated that there is an average elevation of only about 15 per cent with 10 Gm doses of calcium lactate. Hoyle<sup>39</sup> obtained an increase of from 10 to 15 per cent in serum calcium in rabbits given doses of 3 Gm of calcium lactate per kilogram. Liebermann<sup>41</sup> obtained increases of around 70 per cent with doses of 10 Gm of calcium gluconate fed to young human adults, although he stated that the results varied greatly with the individual. Working with dogs, Hjort<sup>43</sup> found an increase in serum calcium with calcium chloride, calcium lactate and calcium glycerophosphate when the dosage was greater than 0.195 Gm of calcium per kilogram of body weight. With calcium lactate at a level of 1.5 Gm per kilogram, Hjort obtained an average increase of about 40 per cent. It is also commonly held that calcium chloride is superior to other salts in increasing the level of serum calcium because of its acidotic effect<sup>44</sup>.

Since all the investigations cited suffer from the defect that there has been considered only the change produced in the total calcium of

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38 Bauer, W., and Ropes, M. W. Effect of Calcium Lactate Ingestion on Serum Calcium, *J A M A* **87** 1902 (Dec 4) 1926

39 Hoyle, J. C. Studies in Serum Calcium. Oral Administration, *J Pharmacol & Exper Therap* **32** 309, 1928

40 Rothlin, E. Experimentelle Untersuchungen über Resorption und Wirkungsweise des gluconsauren Calciums, *Ztschr f d ges exper Med* **70** 634, 1930

41 Liebermann, A. L. Studies on Calcium. Blood Calcium Changes Following Administration of Calcium Gluconate Given Subcutaneously to Normal and Parathyroidectomized Dogs and per Os to Human Beings, *J Pharmacol & Exper Therap* **42** 245 (June) 1931

42 Jansen, W. H. Kalkstoffwechsel, Blutkalkgehalt und Kalkwirkung, *Klin Wchnschr* **3** 715, 1924

43 Hjort, A. M. Influence of Orally Administered Calcium Salts on Serum Calcium of Normal and Thyreoparathyroidic Dogs, *J Biol Chem* **65** 783 (Oct) 1925

44 Stewart, C. P., and Percival, G. H. Calcium Metabolism, *Physiol Rev* **8** 283, 1928

the serum as a result of the ingestion of calcium salts, we have carried out a series of experiments to obtain the time curves for the diffusible calcium, nondiffusible calcium and inorganic phosphate as well, using both human subjects and dogs for the experiments. The experimental procedure was much the same as for the experiments on the ingestion of milk, the calcium salts being given with liberal quantities of water. The results that were obtained are illustrated by the curves given in charts 6 to 10, in which there are plotted the data of representative experiments for each of the calcium salts employed. In these curves there are shown the changes in total calcium, diffusible calcium, nondiffusible calcium and inorganic serum phosphate after the ingestion of a calcium salt. To economize space, only the results obtained on dogs are included here, since the results on the human subjects are quite similar.

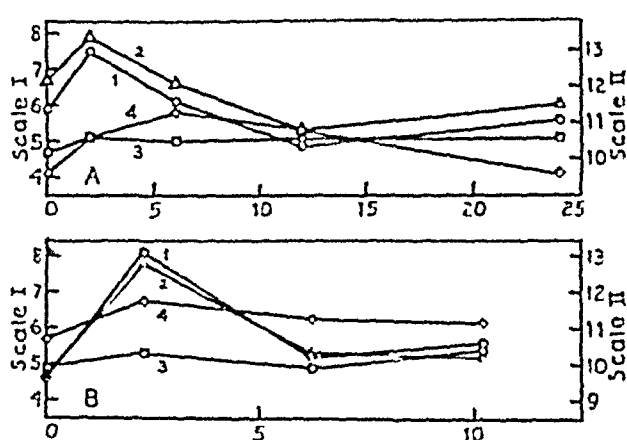


Chart 6—*A*, curves for calcium fractions and inorganic phosphate fractions after ingestion of 7 Gm of calcium chloride (dog E, weighing 14 Kg). The chart shows the features usually obtained, an increase in serum calcium with a maximum at about two hours, which is due solely to the increase in the diffusible calcium, the nondiffusible calcium remaining within experimental error unaltered during the experiment. The inorganic serum phosphate also increases and reaches a maximum in about six hours. *B*, another experiment with calcium chloride (12 Gm), showing the usual features except that the phosphate maximum is reached in two hours (dog 2, weighing 17 Kg).

Our results for the change in total serum calcium agree with the sequence of events obtained by Hjort. If no emesis or diarrhea occurred, there was produced a considerable increase in serum calcium, the maximum ordinarily coming about two hours after the ingestion of the salt. We were, however, unable to confirm the point of view that there are exceptional differences in the efficiency of effect among the soluble calcium salts that we employed, including calcium chloride. Rather, the observations are in better harmony with the view that the increase in blood calcium is proportional to the calcium content of the

dose employed, irrespective of which salt is employed. This is graphically shown by chart 5, in which there are plotted the maximal increases in the total serum calcium obtained in the experiments with dogs with calcium chloride, acetate, lactate and gluconate. In this chart the maximum increase obtained in serum calcium, in milligrams per hundred cubic centimeters, for each experiment is plotted against the calcium content of the dose of the salt employed. While there is a considerable scattering of some of the points, the general trend favors a proportionality between the level of increase and calcium dosage not dependent on the particular salt. The line drawn through the points in the charts shows that with a dose of calcium of 2 Gm, which corresponds to about

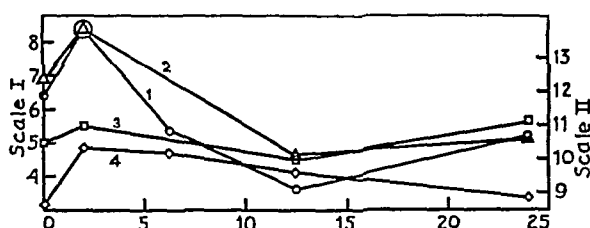


Chart 7—An experiment with calcium lactate (10 Gm) showing the same features as were obtained with calcium chloride (dog B, weighing 13.5 Kg)

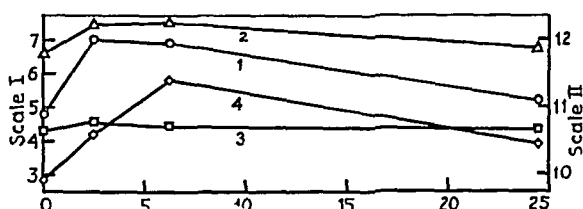


Chart 8—The results obtained on the ingestion of 15 Gm of calcium gluconate (dog 4, weighing 22 Kg), again illustrating that the increase in the serum calcium is due solely to an increase in the diffusible calcium while the nondiffusible calcium remains unaltered. The results show the typical features of the maximum of the calcium increase at two hours and the maximum of the phosphate increase at six hours.

7 Gm of calcium chloride, 8 Gm of calcium acetate, 11 Gm of calcium lactate and 22 Gm of calcium gluconate, there was obtained an average increase of 15 mg per hundred cubic centimeters, which represents approximately a 15 per cent increase in serum calcium. While the response is largely dependent on the dose of calcium, our results agree better with the authors who report only moderate increases in serum calcium.

It is of great interest and particularly to be noted that the change in the serum calcium is a result of the change in the diffusible calcium which mirrors the change in total calcium almost exactly, while the non-

diffusible calcium, except for what are probably experimental errors, remains unchanged throughout the whole cycle of events. The whole of the absorbed calcium which determines the increase in the blood calcium level over this period of about four hours remains in a diffusible condition, undergoing no reaction with the plasma proteins to become partially converted to the nondiffusible calcium. From what was stated in the introduction it follows that all this extra calcium should be expected to remain physiologically active.

The behavior of the inorganic serum phosphate is another point of great interest. Along with the change in calcium there takes place a

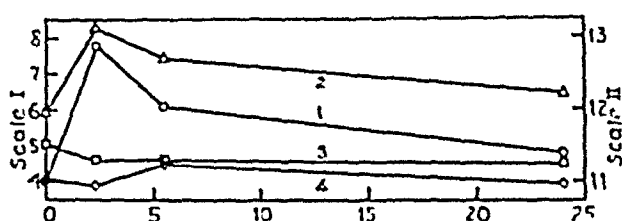


Chart 9—Another experiment with calcium gluconate (16.5 Gm.) in which the serum calcium increase was greater (dog 4, weighing 22 Kg.). The chart confirms the typical response in the calcium fractions found on the ingestion of calcium salts.

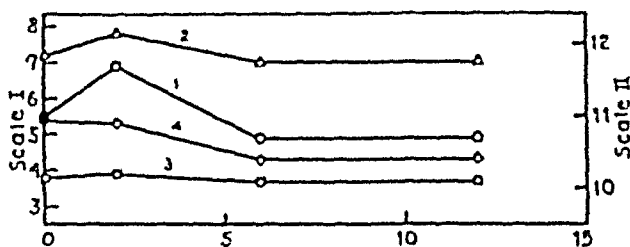


Chart 10—An experiment with calcium acetate (6 Gm.), showing the usual features obtained with the other calcium salts except for a drop in the inorganic phosphate (dog L, weighing 20 Kg.).

characteristic sequence of change in the serum phosphate. The phosphate increases along with the calcium, usually to a value of about 1 mg per hundred cubic centimeters. The sequence of change, however, does not coincide with that of the calcium, since the increase is maintained for a much longer period, lasting about six hours and then slowly falling back to the initial value.

*Effect of the Injection of Parathyroid Extract*—In 1925, Collip announced the isolation of a potent extract from beef parathyroid glands with the power of being able strongly to increase the level of the serum calcium in parathyroidoprival and in normal animals. Since the announcement the biochemical influence of Collip's and other similar extracts has



been extensively studied by Collip and his collaborators<sup>45</sup> and by other workers<sup>46</sup>

The majority of the studies have been concerned with the change in total serum calcium only, but unlike those studying other calcium-influencing agencies, several authors have investigated the changes undergone by the diffusible and nondiffusible calcium, among these are Moritz,<sup>46d</sup> working on rabbits, and Snell,<sup>46e</sup> working on dogs. When the present work was undertaken, Snell's paper had not yet been published and only Moritz' studies were available. Since there are a number of objections to using rabbits as subjects for studies of blood calcium because of their marked insensitivity to factors affecting the blood calcium, and since Moritz' experiments show only small increases in the serum calcium, experiments were planned and carried out on the effect of injections of parathyroid extract on the total calcium, diffusible calcium, nondiffusible calcium and inorganic phosphate of serum, using dogs as experimental subjects. The time curves of representative results with single doses of parathyroid extract are given in chart 11 *A* and *B*, and the curves for the effect of a repeated dose are shown in chart 11 *C*. For these experiments, Collip's parathyroid extract was used, the injections being given subcutaneously.

On injecting a single dose of from 100 to 200 units of parathyroid extract-Collip, the maximum of the increase was found to be at about the twenty-fourth hour. This is not in agreement with Collip, Clark and Scott,<sup>45a</sup> who stated that the maximum level under such conditions is obtained in from five to nine hours. Furthermore, the return to the normal calcium values in our experiments required about seventy-two hours as against about fifteen hours found by Collip, Clark and Scott. Just what the reasons are for the differences in the behavior between our animals and those of Collip, Clark and Scott we are at a loss to explain. In only two instances in fifteen experiments carried out was

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45 (a) Collip, J. B., Clark, E. P., and Scott. Effect of a Parathyroid Hormone on Normal Animals, *J. Biol. Chem.* **63** 439 (March) 1925. (b) Collip, J. B. The Parathyroid Glands, *Medicine* **5** 1 (Feb.) 1926.

46 (a) Albright, F., Bauer, W., Ropes, M., and Aub, J. C. Studies of Calcium and Phosphorus Metabolism. Effect of Parathyroid Hormone, *J. Clin. Investigation* **7** 139, 1929. (b) Hjort, A. M., Robison, S. C., and Tendick, F. H. Extract Obtained from External Bovine Parathyroid Glands Capable of Inducing Hypercalcemia in Normal and Parathyroidectomized Dogs, *J. Biol. Chem.* **65** 117 (Aug.) 1925. (c) Berman, L. Effect of Protein-Free Acid-Alcohol Extract of Parathyroid Glands upon Calcium Content of Blood and Electrical Irritability of Nerves of Parathyroidectomized and Normal Animals, *Am. J. Physiol.* **75** 358 (Jan.) 1926. (d) Moritz, A. R. State of Serum Calcium in Experimental Hypo- and Hypercalcemia, *J. Biol. Chem.* **66** 343 (Dec.) 1925. (e) Snell, A. M. Diffusibility of Calcium in Blood Serum Under Normal and Pathological Conditions, *Proc. Staff Meet., Mayo Clin.* **5** 17 (Jan. 22) 1930.

the maximum increase obtained in less than twenty-four hours, one of these two exceptions occurring at six hours and the other at thirteen hours

Of marked interest are the curves for the diffusible and nondiffusible calcium. When the blood calcium level is increased by an injection of parathyroid extract, the increase is reflected in both the diffusible and the nondiffusible fractions, while, as shown, when the increase is produced by a calcium-containing compound, the increase takes place only in the diffusible calcium. The increase in both fractions of the calcium after the injection of parathyroid extract-Collip agrees with the findings of

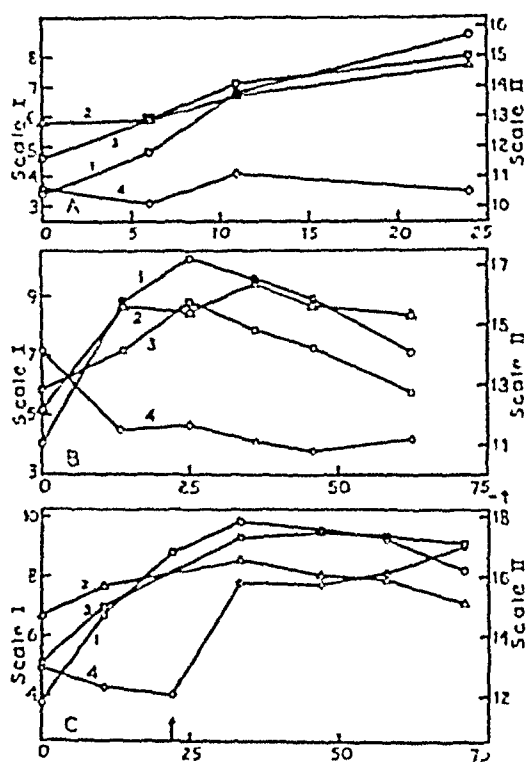


Chart 11—*A*, changes in the calcium fractions and inorganic serum phosphate after the injection of 100 units of parathyroid extract-Collip (dog 3, weighing 15 Kg), showing the continual increase in calcium up to twenty-four hours. The increase is about equally divided between diffusible and nondiffusible calcium. The drop in the inorganic serum phosphate is not as pronounced as is usually the case. *B*, effect of the injection of 150 units of parathyroid extract-Collip (dog 4, weighing 25 Kg), showing the added response for the extra amount of parathyroid extract. The chart illustrates the significant features of the maximum of response in about twenty-four hours, the slow return to normal, the distribution of the increase in calcium about equally between the diffusible and nondiffusible calcium and the drop in inorganic serum phosphate as the calcium increases. *C*, effect of the injection of a repeated dose of parathyroid extract-Collip (dog B, weighing 22 Kg). Each of the two doses consisted of 100 units, the time of the injection of the second dose is indicated by the arrow. The effect on calcium noted here is little different from that of a single injection, except for the prolongation in the time of the increased serum calcium. After the second injection the inorganic phosphate shows the increase that is associated with an overdose of parathyroid extract.

Moritz <sup>46d</sup> and Snell <sup>46e</sup> The increased calcium is about equally divided between the two fractions This is readily seen in the charts When a second dose of the extract is given before the calcium returns to its initial value, the serum calcium goes to still higher levels, as has been shown by Collip, Clark and Scott In chart 11 *C* are given the curves for the effect of a repeated dose of parathyroid extract These show that the extra increase in total calcium is also distributed between diffusible and nondiffusible calcium With a repeated dose, it is seen that the calcium level remains heightened for a considerably longer time than with a single dose

The behavior of the serum inorganic phosphate is no less interesting than that of the diffusible and nondiffusible calcium fractions When

TABLE 2—*The Effect of Repeated Injections of Parathyroid Extract-Collip, Long Intervals Apart, in Dog 3\**

Date	Dose, Units	Initial Values				Time of Maximum Increase, Hrs	Maximum Values			
		Total Calcium	Diffusible Calcium	Non diffusible Calcium	Phosphorus		Total Calcium	Diffusible Calcium	Non diffusible Calcium	Phosphorus
Jan 14	100	10.4	5.80	4.60	3.55	24	15.70	7.70	8.00	3.50
Feb 15	100	11.6	6.10	5.50	4.75	25	15.80	7.80	8.00	3.30
Feb 25	200	10.7	6.10	4.60	4.75	24	16.80	8.40	8.40	2.90
April 5	150	11.8	5.60	6.20	4.15	35	17.80	9.00	8.80	4.65
April 22	150	10.8	6.20	4.60	3.70	13	14.70	8.70	6.00	3.00

\* Analytic figures in milligrams per hundred cubic centimeters of serum

an increase in blood calcium was produced by the administration of a calcium salt, there was found a concomitant increase in inorganic serum phosphate which persisted even longer than the increased calcium level When the blood calcium was increased by the injection of from 100 to 200 units of parathyroid extract-Collip the serum phosphate did not increase Instead, it dropped, as is shown in the charts A drop of this type is to be noted in some of the curves given by Collip <sup>45b</sup> but without comment This observation has also been made and extensively discussed by Albright, Bauer, Ropes and Aub <sup>46a</sup> and by Albright, Bauer, Cockrill and Ellsworth <sup>47</sup> The extent of the drop in the phosphate, it is to be noted, depends on its initial value When this is high, as in experiment 15, in which it was a little over 7 mg per hundred cubic centimeters, the drop is considerable—to 4.5 mg per hundred cubic centimeters With initially low values of serum phosphate, the drop is small

47 Albright, F, Bauer, W, Cockrill, J R, and Ellsworth, R Studies on Physiology of Parathyroid Glands Relation of Serum Calcium to Serum Phosphate at Different Levels of Parathyroid Activity, *J Clin Investigation* 9:659 (Feb) 1931

or may even be absent Albright, Bauer, Ropes and Aub<sup>46</sup> stated that when the serum calcium rises above a critical level of about 15 mg, the blood phosphorus rises With dogs we did not find this to be so, when the drop persisted at values of over 17 mg per hundred cubic centimeters However, when a repeated dose of parathyroid extract-Collip was given, as in the experiment recorded in chart 11 C, a rise of the phosphate did take place This rise in phosphate has been thoroughly discussed by Collip<sup>45b</sup> as an important factor in the phenomenon of overdosage with parathyroid extract discovered by him

The effect of the periodic injection of doses of parathyroid extract-Collip is of interest The results of such a series carried out at various intervals during a three month period are given in table 2 The table shows no particularly persistent influence of the repeated injections over the periods in which the parathyroid extract was given

In some of the periods the response does not appear to be proportional to the dosage of parathyroid extract, but it is not possible from these results to argue justifiably that there is an increasing loss of susceptibility to the parathyroid extract with the repeated injections when there is a lapse of several weeks between each injection

#### COMMENT

The most significant observations in the experimental work are the contrasts in the effects produced when the level of the blood calcium is increased by a calcium-containing compound and by the injection of parathyroid extract-Collip With a soluble calcium compound, the increase is solely in the diffusible calcium fraction and there is a concomitant increase in inorganic serum phosphate, while when the calcium increase is induced by parathyroid extract the two calcium fractions both share in the increase and the inorganic serum phosphate decreases These observations show that the actual mechanism of the factors governing the interrelation of diffusible calcium, nondiffusible calcium and inorganic phosphate of the blood *in vivo* is more complex than the picture outlined in the introduction

It might be pointed out that so far nothing has been said of the changes undergone by the serum proteins during these experiments, if they were taken into account, the results would perhaps fit better into the mechanism just mentioned Actually, such is not the case Serum proteins were determined in many of the experiments by the method of one of us (D. Greenberg<sup>48</sup>), and the proteins, including both the albumin and the globulin, were found to remain unchanged throughout the course of an experiment One point that may be an important factor in the difference in behavior is the time The changes in calcium are over

48 Greenberg, D. M. Colorimetric Determination of Serum Proteins, *J. Biol. Chem.* 82: 545 (May) 1929

within about four hours after the ingestion of a calcium salt, and they only reach their maximum twenty-four hours after the injection of parathyroid extract-Collip

Little more can be said than this at present concerning the nature of the different behavior. The action of parathyroid extract fits in well with the mechanism pictured in the introduction. As the blood calcium increases, the increase is distributed according to some equilibrium between diffusible and nondiffusible calcium, the level of the nondiffusible calcium being determined by the serum protein content. Also, with an increase in diffusible calcium, if the solubility product of a calcium salt determines the relation between the calcium and the phosphate ion, the inorganic serum phosphate should decrease, as it actually is found to do.

On the contrary, the changes observed after the ingestion of a calcium salt are at present unexplainable on the hypothesis laid down in the introduction, unless the duration of the increase in calcium is too short a period to allow an equilibrium between diffusible calcium and inorganic phosphate and diffusible calcium and nondiffusible calcium to be established. Otherwise, it does not seem possible to reconcile the fact that only the diffusible calcium increases, while the inorganic phosphate content, instead of decreasing, rises, with the current theories of the mechanism that determines the level of blood calcium.

#### SUMMARY

1 An experimental study has been carried out on the changes produced in the diffusible calcium, nondiffusible calcium and inorganic phosphate of the serum by certain agents that are capable of affecting the level of the blood calcium.

2 Criticisms directed against the determination of diffusible calcium have been considered, and it is pointed out that the method used by us has given reproducible and concordant results, not only in our own hands, but in the hands of many investigators in widely separated laboratories.

3 In a dog with a bile-renal fistula in which there was complete elimination of bile from the body, there was found to be little change in total and diffusible calcium during a period of about two months, contrary to the claims made by Emerson<sup>14</sup>.

4 During short periods of fasting, no marked changes were found to take place in the calcium and inorganic phosphate of the serum, indicating that there is no daily rhythm of change in the calcium fractions and phosphate of the blood.

5 In experiments on the ingestion of milk by human subjects, marked differences in the effect produced were found between sweet and acidified milk. When 1 liter of sweet milk was ingested, no increase

took place in the blood calcium—in fact, there was usually a slight decrease. The inorganic serum phosphate in these experiments ordinarily increased. With the ingestion of 1 liter of acidified milk, on the other hand, an increase took place in both the calcium and the phosphate, the maximum of the increase coming about eight hours after the ingestion of the milk. The increase amounted to about 1 mg of calcium per hundred cubic centimeters of serum, and was due to an increase in the diffusible fraction, the nondiffusible calcium remaining unchanged.

6 The increase of the serum calcium in dogs on the oral ingestion of calcium chloride, lactate, acetate and gluconate was found to be the same for all of these salts, when given in equivalent quantities. The increase in calcium was found to be proportional to the calcium content of the dose of the salt. No special efficacy in increasing blood calcium was found with any of these calcium salts.

7 When the blood calcium was increased by the ingestion of calcium, chloride, lactate, acetate or gluconate, the maximum of the increase occurred about two hours, and the blood calcium returned to the initial value in about four hours, after the ingestion of the salt. The inorganic serum phosphate also increased, the increase being about 1 mg per hundred cubic centimeters, regardless of the dose of calcium. The maximum increase in phosphate came after the calcium content had dropped to normal, namely, in about six hours.

*The total increase in the serum calcium after the ingestion of a calcium salt is due to an increase in the diffusible calcium fraction alone, while the nondiffusible calcium remains unaltered throughout the experiment.*

8 When single doses of parathyroid extract-Collip of from 100 to 200 units were injected subcutaneously into dogs weighing from 15 to 25 Kg, the increase in serum calcium was found to require about twenty-four hours to reach the maximum and about seventy-two hours to fall back to the initial value. With parathyroid extract-Collip the increase in calcium was found to be due to an increase in both the diffusible and the nondiffusible fractions, the amount of the increase being about equally divided between the two fractions. The inorganic serum phosphate in these experiments showed a drop from the initial values. When a repeated dose of parathyroid extract-Collip is given at about the point of the maximum of the first, the extra increase in calcium has about the same features as for a single dose.

# CHEMISTRY AND METABOLISM IN EXPERIMENTAL YELLOW FEVER IN MACACUS RHESUS MONKEYS

## VI THE BROMSULPHALEIN LIVER FUNCTION TEST AND THE VAN DEN BERGH REACTION

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In previous articles<sup>1</sup> it has been shown that there is a definite decline in hepatic function during the course of yellow fever. This loss of function makes itself evident about twenty-four hours before death (in some cases earlier), through alterations in the fasting blood sugar and in the blood sugar curves following the injection of dextrose. In the later stages of the disease, usually during the last ten or twelve hours before death, there are marked changes in the nitrogen metabolism and in some of the mineral elements of the blood and the urine.

In this paper are presented the results of further tests for hepatic function: (1) the bromsulphalein liver function test, (2) determination of the bilirubin content of blood by the van den Bergh reaction and (3) a number of examinations made for fibrin and the coagulation time of the blood. The bromsulphalein liver function test was performed by the technique described by Rosenthal and White<sup>2</sup>. Five milligrams of the dye per kilogram of body weight was injected intravenously. The bilirubin content of the blood was determined by the van den Bergh reaction as described by McNee<sup>3</sup>. The coagulation time of the blood was determined by Lee and White's method<sup>4</sup>. The fibrinogen in the

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1 Wakeman, A. M., and Morrell, C. A. (a) Chemistry and Metabolism in Experimental Yellow Fever. I. Concentration of Nonprotein Nitrogenous Constituents in the Blood, *Arch. Int. Med.* **46**: 290 (Aug.) 1930, (b) II Nitrogen Metabolism, *ibid.* **46**: 382 (Sept.) 1930, (c) III Blood Sugar and Liver Glycogen, *ibid.* **47**: 104 (Jan.) 1931, (d) IV Tolerance Tests for Dextrose, *ibid.* **48**: 301 (Aug.) 1931, (e) V Acid-Base and Electrolyte Equilibrium, *ibid.* **49**: 826 (May) 1932.

2 Rosenthal, S. M., and White, E. C. Clinical Application of Bromsulphalein Test for Hepatic Function, *J. A. M. A.* **84**: 1112 (April 11) 1925.

3 McNee, J. W. Jaundice. Review of Recent Work, *Quart. J. Med.* **16**: 390 (July) 1923.

4 Todd, J. C., and Sanford, A. H. Clinical Diagnosis by Laboratory Methods, Philadelphia, W. B. Saunders Company, 1927, p. 228.

plasma was estimated from the difference between the protein content before and after the removal of fibrinogen with calcium chloride <sup>5</sup>

## EXPERIMENTAL METHODS

1 *Van den Bergh Determinations*—Chart 1 presents the results of forty-nine determinations of bilirubin. Four of these were made on normal monkeys and the remainder on monkeys in various stages of

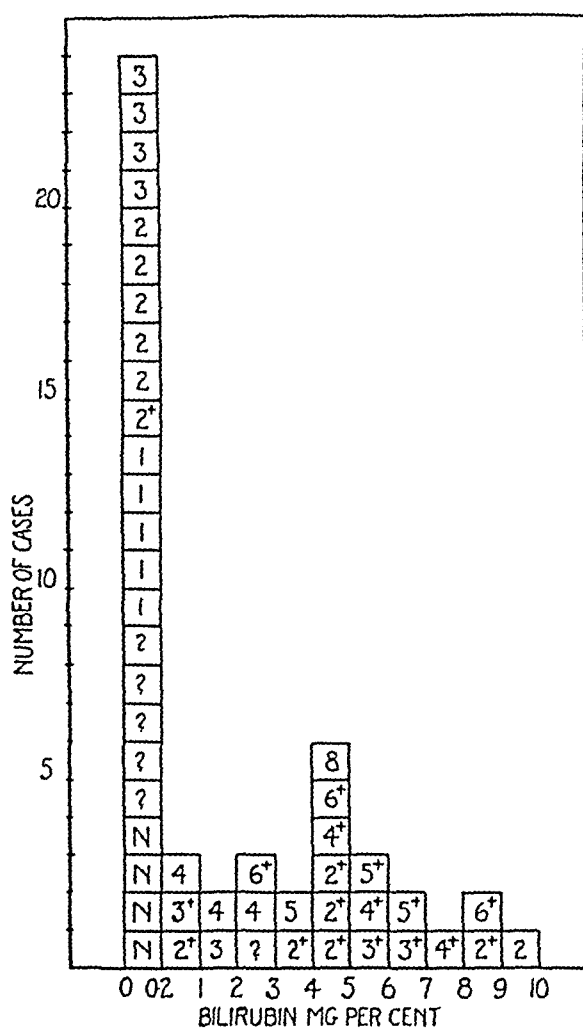


Chart 1—Blood bilirubin in yellow fever The number in a square indicates the day of fever on which the sample of blood was taken A question mark signifies that the day of fever is unknown *N* signifies a normal monkey + signifies that the monkey died within ten hours after the sample of blood was taken

yellow fever. Monkeys with only a trace (up to 0.2 mg per hundred cubic centimeters) of bilirubin in the serum are presented in the first column. This column includes figures obtained from normal monkeys, the majority of the remainder are from animals in the early stages of

<sup>5</sup> Hawk, P. B., and Bergeim, Olaf. Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son & Co., 1927, p. 398.



yellow fever One animal died on the second day of fever with less than 0.2 mg of bilirubin per hundred cubic centimeters of blood The course of illness in this animal was short Death occurred on the third day after inoculation, when the blood serum contained 15.7 mg of inorganic phosphorus and 94 per cent of nonprotein nitrogen, and when the blood sugar was only 25 mg These abnormalities suggest a considerable loss in hepatic function<sup>6</sup> Two other monkeys died with a serum bilirubin content of less than 1 mg Only 15 per cent of the animals (five of thirty-four) died with a van den Bergh value of less than 4 mg

No correlation was observed between the length of the febrile period and the degree of jaundice In four cases, monkeys in the third day of fever had no more than a trace of pigment in the serum, while the monkey showing the highest amount of pigment in the serum was in the second day of fever

2 *Bromsulphalein Liver Function Tests*—Dye was injected into twelve monkeys Three of these were normal monkeys that were not later infected with yellow fever Several animals were given injections on consecutive days of the disease, and alterations in their ability to excrete the dye were noted Results of these experiments are recorded in chart 2 The curves obtained from the three normal monkeys and from monkeys M1, M2 and M3 during the control period indicate a rapid withdrawal of the dye from the blood of the normal *Macacus rhesus* Only small quantities were found in the blood ten minutes after injection A progressively increasing retention in the course of the disease is illustrated by monkeys M1, M2, M3, M6, M7 and M8 The excretion was abnormally slow in all cases of yellow fever

Differences in the rate of progress of the disease are demonstrated by monkeys M1, M3, M7 and M8 In M1 and M3 there was only a slight abnormal retention on the second day of fever, while in M7 and M8 retention was almost complete on the corresponding day The illness was much shorter in the latter two monkeys and terminated fatally on the fourth and third days, respectively, after inoculation Considerable retention occurred in monkeys M7 and M8 on the day following infection, before any febrile reaction was evident In *Macacus rhesus* M1 marked retention of the dye did not occur until the fifth day of fever The animal died on the following day

3 *Fibrin and Clotting Time of the Blood*—The average clotting time of normal monkey blood (fourteen cases) determined by Lee and White's method,<sup>4</sup> at room temperature (from 80 to 95 F), was slightly less than two and one-half minutes, with a minimum of one and one-half minutes and a maximum of four minutes In eleven of the cases studied, the coagulation time during yellow fever was greater than the

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<sup>6</sup> Wakeman and Morrell <sup>12</sup> b c

normal average, the greatest increases being on the second day of the fever or later. In one case the clotting time decreased as the fever progressed, while no change was observed in the remaining two cases.

Determinations of blood fibrin were made on eight monkeys. From these, only three values were obtained, from presumably normal animals. Expressed as milligrams of fibrin nitrogen per hundred cubic centimeters

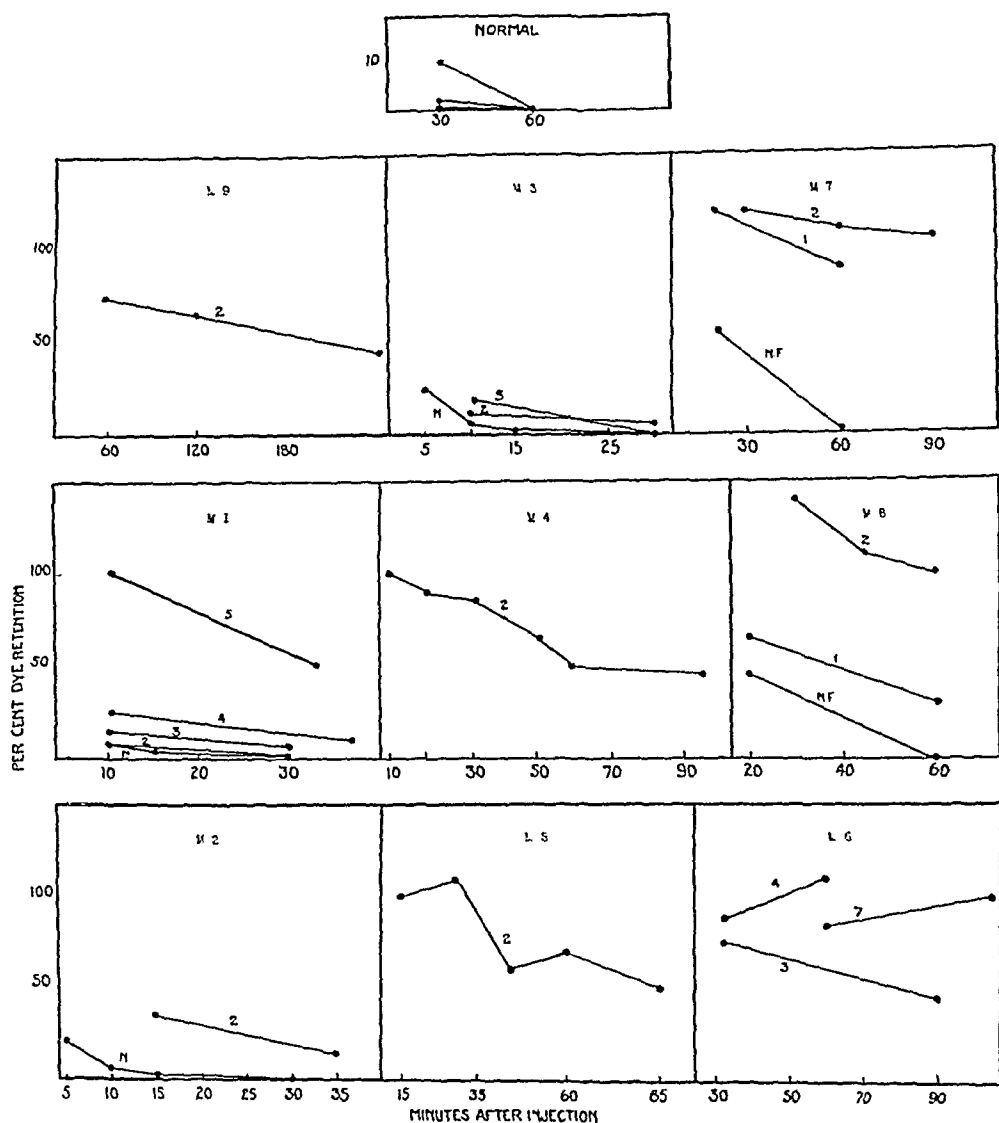


Chart 2—Bromsulphalein tests in yellow fever. The numbers beside the curves indicate the day of fever on which the test was performed. *NF* signifies that the monkey was infected but had not yet shown fever. *N* signifies that the monkey had not yet been infected.

of plasma, these were 35, 72 and 138. Values determined on the first day of fever were in every case larger than these, ranging from 199 to 213 mg. The fibrin nitrogen in the blood of two monkeys that died on the fourth and fifth days of fever was 14 and 39 mg, respectively. Three other animals died on the first and second days of fever with from 128 to 213 mg of fibrin nitrogen in the blood.

The fragility of red blood cells in monkeys with yellow fever did not differ significantly from that in the normal monkey

#### COMMENT

A considerable increase in the quantity of bilirubin in the blood occurred in most of the monkeys during yellow fever (chart 1). Values obtained from normal serum, which were recorded as zero or faint traces, have been included in the first column of the chart. Only one animal died with less than 0.2 mg of bilirubin per hundred cubic centimeters of blood. Large variations were found in the amount of pigment in the blood just before death. The figures range from 0.2 to more than 8 mg, while occasionally 2 mg or more was found several days ante mortem. No correlation was found between the length of the febrile period and the amount of bile pigment. One monkey with a fever protracted as long as six days died with less than 3 mg of bilirubin in the blood, while another had more than 9 mg on the second day of fever (chart 1). Excretion of bile pigment is similar to other functions of the liver in this respect,<sup>6</sup> as the degree of functional loss does not depend on the duration of the illness. However, the accumulation of bile pigments in the blood was noted in most cases before other abnormalities became evident. In five cases in which daily observations were made, increases in the bilirubin content of the blood were noted from one to four days before death.

Only one monkey which passed safely through the disease was studied. Three observations were made, one on the first and one on the fourth day of fever, and one on the seventeenth day after inoculation, when the animal had recovered. No increase in bile pigment was noted except for a faint trace which occurred on the fourth day of fever. It is possible that any appreciable accumulation of bilirubin in the blood indicates a fatal prognosis. Klotz and Simpson<sup>7</sup> have pointed out that patients may die of yellow fever with little or no jaundice occurring. The one monkey that died with less than 0.2 mg of bilirubin, as well as two others that showed less than 1 mg of bilirubin, may be classed with cases of this type. Estimations of amino-acid nitrogen, nonprotein nitrogen and sugar in the blood of these monkeys indicated a loss of hepatic function considerably greater than one would infer from the accumulation of bile pigments. Klotz and Simpson ascribed this phenomenon to an inhibited formation of bile pigment due to damage to the reticulo-endothelial system.

Considerable variability was shown in the different types of the van den Bergh reaction observed. The reactions ranged from the

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<sup>7</sup> Klotz, O., and Simpson, W. Jaundice and Liver Lesions in West African Yellow Fever, *Am J Trop Med* 7:271 (Sept) 1927.

indirect, through the biphasic, to the immediate direct type. In general the indirect van den Bergh reaction was obtained early in the course of the disease when the bilirubin content of the blood was low, and became immediate and direct as the bilirubin increased.

The results of the bromsulphalein liver function tests (chart 2) give further evidence of loss of hepatic function in the disease. An abnormally high retention of the dye is among the earliest manifestations of the hepatic lesions produced by yellow fever. In monkeys M7 and M8 such retention occurred while the temperature and blood sugar were in the normal range. In the cases of these two animals the abnormality in the excretion of dye was accompanied by a difficulty in disposing of injected dextrose, although the fasting blood sugar remained normal until the last day of life.<sup>1d</sup> In monkeys M1, M3 and M5 tests were made more than twenty-four hours ante mortem, and marked losses in their ability to excrete the dye appeared a considerable time before any other evidence of progress of the disease was apparent. That changes occur in the ability of the liver to remove the dye from the blood many days before death is shown in the data for monkeys M1, M3, M6, M7 and M8 (chart 2). *Macacus rhesus* M6 showed a high retention as early as four and a half days before death. The first curve from this animal was obtained on the third day of fever, four days after inoculation. Although the dye retention was abnormally high, the nonprotein nitrogen, urea, amino-acid and blood sugar were normal. The blood sugar remained normal until three days later, when it dropped to 41 mg per hundred cubic centimeters twenty-six hours ante mortem. The urea and amino-acid nitrogen were unchanged until the last day of life. In this monkey an impaired excretion of dye was demonstrated before other changes took place. Similarly, in monkeys M1, M2, M3, M7 and M8 the blood sugar remained normal after the rate of excretion of bromsulphalein had decreased. The blood sugar was the first of the substances previously reported to respond to changes in hepatic function during yellow fever. An alteration in the blood sugar was noted as early as fifty hours before death,<sup>1e</sup> but in every case presented in chart 2 this was preceded by an abnormal retention of dye.

An increased coagulation time of the blood during yellow fever has been noted in cases in human beings. Some evidence has been presented here that the blood of *Macacus rhesus* monkeys also clots more slowly during the disease. The results of the determinations of blood fibrin suggest that the increased clotting time may be the result of a decrease in blood fibrinogen. The effect of blood calcium has been ruled out, since no significant changes were found in the calcium content of the blood during yellow fever.<sup>1e</sup> The fibrinogen content of the blood was found to increase during the first days of fever, but when fever was prolonged until the third and fourth days or beyond, the animals died

with a low blood fibrinogen McMaster and Drury<sup>8</sup> and Foster and Whipple<sup>9</sup> have ascribed to the liver the origin of blood fibrinogen. Destructive lesions produced by yellow fever may, in the early stages of the disease, stimulate the formation of fibrinogen, while in the longer febrile periods the effect of the hepatic lesions may become apparent through decreased blood fibrinogen.

Himwich, Goldfarb and Weller<sup>10</sup> have recently demonstrated that the liver is the chief site of acetone production. These investigators, working with depancreatized dogs, based their conclusions on the acetone content of blood entering and leaving such organs as the liver, muscle, kidney and the viscera drained by the portal vein. In the present studies of experimental yellow fever a number of qualitative tests for acetone in the urine were made by means of the sodium nitroprusside reaction. The specimens of urine tested were from monkeys that had shown a low blood sugar for a considerable period before death. No positive test for acetone was obtained from the urine of these monkeys. On the other hand, the urine of *Macacus rhesus* M14, which was starved for twenty-eight days, showed from 2+ to 4+ acetone from the eleventh to the twenty-sixth day of starvation. These were the only days on which the test was performed. It is significant that monkeys dying of yellow fever and in a condition of carbohydrate starvation, with the blood sugar as low as 25 mg for some time, excreted no acetone in the urine. All the evidence from this series of studies indicates that the liver is without normal function in the terminal stages of yellow fever. Hence, if the liver is the chief site of acetone production, little or no acetone should be present in the urine of moribund monkeys. This was found to be the case.

#### SUMMARY

1 The rate of excretion of bromsulphalein dye by the liver is greatly diminished in yellow fever. An abnormally great retention of the dye by infected monkeys is observed in many cases several days before death.

2 The onset of jaundice during yellow fever is manifested by an increase in the bilirubin content of the blood. The increased retention of bile pigment in the blood may begin several days before death.

3 Increasing amounts of bile pigment in the blood and, more especially, abnormally slow removal of bromsulphalein dye from the blood

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8 McMaster, P. D., and Drury, D. R. The Source of Fibrinogen, *Proc Soc Exper Biol & Med* **26** 490 (March) 1929.

9 Foster, D. P., and Whipple, G. H. Fibrin Values Influenced by Cell Injury, Inflammation, Intoxication, Liver Injury, and the Eck Fistula. Notes Concerning the Origin of Fibrinogen in Body, *Am J Physiol* **58** 407 (Jan) 1922.

10 Himwich, H. E., Goldfarb, W., and Weller, A. Effect of Various Organs on Acetone Content of Blood in Phlorhizin and Pancreatin Diabetes, *J Biol Chem* **93** 337 (Oct) 1931.

are the first indications of loss of hepatic function in monkeys suffering from yellow fever

4 Some evidence is presented showing that the clotting time of blood is usually prolonged in yellow fever

5 The increased clotting time is associated with a lowered fibrinogen content of the blood

6 Monkeys dying of yellow fever do not excrete acetone in the urine This fact supports the evidence that the liver is the chief site of acetone formation

# THROMBO-ANGIITIS OBLITERANS AMONG WOMEN

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Thrombo-angitis obliterans usually affects men between the ages of 20 and 45 years. Although approximately seven hundred cases of thrombo-angitis obliterans have been observed at the Mayo Clinic, the present report of ten cases is the first series among women to be put on record. The diagnosis in three of these cases was proved by a study of the pathologic changes in the occluded arteries and veins. Only three acceptable cases have been reported in the literature (cases 1, 2 and 3). In 1924, Buerger<sup>1</sup> made a clinical diagnosis of the condition of two women without proof of pathologic changes. In 1925, Meleney and Miller<sup>2</sup> reported that they had observed a Chinese woman with thrombo-angitis obliterans, their study of the occluded vessels leaves no doubt as to the diagnosis. Koyano<sup>3</sup> reported the case of a woman, aged 55, in whom a peculiar vascular disturbance had appeared in the left leg following influenza, necessitating amputation. Data are inadequate to substantiate the diagnosis of thrombo-angitis obliterans. Telford and Stopford<sup>4</sup> reported two cases of occlusive vascular disease in women, but in our opinion these did not represent cases of thrombo-angitis obliterans. Trabaud and Chaty<sup>5</sup> reported a case of obscure vascular disturbance in the extremities of a Mohammedan girl, aged 20, which does not conform to that observed in cases of thrombo-angitis obliterans.

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From the Division of Medicine, the Mayo Clinic

1 Buerger, Leo. *The Circulatory Disturbances of the Extremities, Including Gangrene, Vasomotor, and Trophic Disorders*, Philadelphia, W. B. Saunders Company, 1924.

2 Meleney, F. L., and Miller, G. G. A Contribution to the Study of Thrombo-Angitis Obliterans, *Ann Surg* **81** 976 (May) 1925.

3 Koyano, K. A Clinical Study of One Hundred Cases of Thrombo-Angitis Obliterans Among the Japanese, *Acta scholae med univ imp, Kyoto* **4** 489 (April) 1922.

4 Telford, E. D., and Stopford, J. S. B. Two Cases of Thrombo-Angitis Obliterans in Women, *Brit M J* **1** 1140 (June 25) 1927.

5 Trabaud, J., and Chaty, Choukat. Étude microscopique des lésions dans un cas de maladie de Leo Buerger chez une femme musulmane, *Bull et mém Soc méd d hop de Paris* **47** 583 (April 6) 1931. Trabaud, J., and Mredde. Maladie de Leo Buerger chez une jeune fille musulmane, *Bull et mem Soc méd d hop de Paris* **47** 579 (April 6) 1931.

## ABSTRACTS OF CASES REPORTED IN THE LITERATURE

CASE 1 (Buerger) —A Jewess (age not stated) was observed in February, 1912. She gave an indefinite history of right "sciatica" followed from three to four months later by pain in the right foot, coldness, pallor and intermittent claudication.

General examination was negative except for the condition of the right lower extremity. Pulsations could not be felt in the right posterior tibial artery. All of the other peripheral arteries pulsated normally. Moderate rubor of the right foot in the dependent position and moderate ischemia, when the foot was elevated, were noted. The patient was again observed in June, 1912. Shortly after her first examination she received a burn on the right foot, and an ulcer developed under the nail of the right great toe. The nail came off, and the nail bed healed in four weeks. A few weeks later, the right foot became badly affected, the toes looked almost black, and amputation of the foot was advised. The nail bed of the right great toe was gangrenous. Amputation was refused, the symptoms in the foot gradually subsided, and healing took place. Pulsations were absent in the right dorsalis pedis and the right posterior tibial arteries. Rubor and blanching of the foot were more marked than at the time of the first examination. The patient was again observed in January, 1913. Both feet were slightly cold. Evidence of atrophy was not present. The right foot showed definite rubor in the dependent position. On elevation, both feet were distinctly blanched. Pulsations could not be felt in the right dorsalis pedis, right posterior tibial and left dorsalis pedis arteries. In June, 1912, the right foot had become distinctly warmer, and the patient considered herself much improved. Examination disclosed the same condition of pulsations as at the previous examination.

The clinical course in this case, with the history of intermittent claudication and evidence of slowly progressing occlusive vascular disease in the right foot, followed later by a similar occlusive vascular process in the left foot, leaves little doubt as to the correct clinical diagnosis of thrombo-angitis obliterans.

CASE 2 (Buerger) —A woman, aged 38 (nationality not stated), began to have pain in the calf of the right leg on walking following an attack of influenza two years previously. The right leg became swollen, but after six months the cramps in the calf disappeared, the swelling, however, persisted, and all the toes were numb. Eight months before examination the right foot had become cold, and the patient had noticed a red spot on the inner aspect of the right leg.

General examination revealed edema of the right foot and leg, more marked over the ankle. The great toe was hemorrhagic, showing evidence of discoloration of the tip with ecchymosis. There was moderate erythromelia over the forepart of the right foot. Elevation elicited considerable ischemia. On a return to the horizontal position, the color did not appear for some time, rubor appeared first above the roots of the toes, and the toes themselves remained ischemic and cyanotic. Pulsations in the dorsalis pedis and posterior tibial arteries of the right foot were absent, those of the left foot were present.

We are inclined to accept this as a true case of thrombo-angitis obliterans, and think that the clinical course justifies this diagnosis. It is possible, however, that this case represents the same type of condition as represented by the case reported by Koyano.



CASE 3 (Meleney and Miller) —In October, 1921, a woman, aged 48, complained of having had severe pain in the right foot for five or six years and ulceration of the distal end of the foot for three years. Five years before examination the great toe had received some sort of trauma. Following this the nail sloughed off, the wound took five months to heal, and the general pain in the foot continued. Two years later all of the toes became black and slowly separated. The bases never healed over. Pain steadily increased. The history was irrelevant except for the fact that the feet had been bound in childhood.

The right foot was small and covered with tight skin. All of the toes were missing, and there was a granulating ulcer in the region of the bases of the toes with a protrusion of the heads of the first and second metatarsal bones. Around the ulcer, the skin had the purplish color of gradually dying tissue. There was no sharp line of demarcation. The dorsalis pedis artery could not be felt. The popliteal artery was palpable, but there was less volume than on the other side. The urine was normal. The Wassermann reaction of the blood was negative. Roentgenograms disclosed decalcification of the bones but no osteomyelitis. The arteries were not visible.

The leg was amputated at the middle. The edges of the wound became gangrenous, and the tissue above became dusky. The wound opened. *Staphylococcus aureus* was recovered in cultures from the fluid. The wound gradually healed in three months. An old obliterating thrombus was found in both the anterior and the posterior tibial arteries with secondary canalization. The dorsalis pedis had not only the old process, but also evidence of a relatively more acute process, as shown by the presence of giant cells.

The clinical course in this case, the closure of the right dorsalis pedis and right posterior tibial arteries, with auto-amputation of all the toes, and the pathologic changes in the arteries and veins in the amputated extremity make the diagnosis of thrombo-angitis obliterans certain.

CASE 4 (Koyano) —A housewife, aged 55, had experienced languor soon after an attack of chills and high fever with fits of coughing in January, 1920 (during an epidemic of influenza). Twelve days afterward she had noticed a dark red spot on the middle of the left leg and cyanosis of the foot, the pain kept her from moving. The spot spread toward the terminus and turned dark brown.

The left leg was amputated at the middle. Histologic examination of one of the internal saphenous veins disclosed an obliterating clot in the early state of the organizing process. In the center of the clot was a so-called purulent focus, similar to that of thrombo-angitis obliterans.

The clinical course in this case does not suggest thrombo-angitis obliterans. The fact that it followed influenza suggests that the lesion in the left leg was acute arteritis rather than the more chronic occlusive arterial lesion such as usually obtains in thrombo-angitis obliterans. The histologic proof of the internal saphenous vein is not convincing. Koyano did not mention the type of lesion that was found in the arteries of the amputated extremity. Notes were not made regarding pulsation in the extremity that was subsequently amputated or in the other extremities.

CASE 5 (Telford and Stopford) —A woman, aged 52, born in England, had had severe aching pain in the index and middle fingers of the left hand for fifteen months. The fingers became slightly blue. Within three weeks the whole hand ached severely, and was cold and dark red. Within three months after the onset of symptoms, dry gangrene of the left hand and the lower part of the forearm developed. The pain then ceased, and no change in the extremity was observed during the following twelve months. For the greater part of her life the patient had worked in a dye works with her hands continually in cold, running water.

The heart was normal. The pulse in the head, neck and right arm was normal. Pulsations were absent in the vessels of the left arm. In both lower extremities a slight pulse could be felt in the popliteal artery but at no other point below this. Sensation in the left arm, above the gangrenous area, was normal. The patient died shortly afterward from "malignant ovarian cyst." Specimens of the blood vessels were not obtained for examination.

This is an unusual type of case, but can hardly be called thrombo-angitis obliterans. The presence of a malignant ovarian cyst may well explain many of the vascular phenomena observed.

CASE 6 (Telford and Stopford) —A woman, aged 48, born in England, had first noticed weakness of the left hand six years previously. The weakness progressed, and there were tingling and aching of the forefinger. Within a year, the right arm followed the same course, but the trouble was never so severe.

Both arms were weak and much wasted. There was no alteration of sensation, sign of a nerve lesion, discoloration or other gross evidence of circulatory trouble. Pulsations in the head and neck were normal, but were entirely absent in the upper extremities. The patient stated that her legs tired easily and often "went to sleep." In the right lower extremity a feeble pulse could be felt in all the large vessels, but in the left lower extremity pulsation could not be felt in or below the popliteal artery. The femoral pulse on the right side was very faint. Sixteen years prior to the onset of the patient's present symptoms, pulsations could not be detected in the upper extremities.

We are unable to classify this case. The onset of weakness in the left hand, followed later by marked wasting of both arms, certainly does not suggest the clinical picture observed in thrombo-angitis obliterans.

CASE 7 (Trabaud and Chaty) —A Mohammedan girl, aged 20, entered the hospital because of trophic disturbances of the hands and feet which had been present for four years. Burning and pain in the extremities, nocturnal attacks of pain and attacks of what had been termed hepatic colic associated with jaundice were present. For a period of about a month she had had cyanosis of the fifth finger of the right hand, and this process extended to the fourth finger and then to the third. The same condition appeared in the third finger of the left hand and the fifth toe of the right foot.

Examination disclosed dry gangrene of the third, fourth and fifth fingers of the right hand, and cyanosis of the right index finger and thumb. There was also dry gangrene of the first, third and fifth fingers of the left hand as far as the first joints, and cyanosis of the fourth finger and thumb. Gangrene of the first, second, third and fourth toes of the right foot was present, and cyanosis of the first toe of the left foot, with several bluish plaques on the second toe of the left foot. The disease progressed rapidly. The feet, legs and forearms became cyanotic,

and gangrene appeared on the tip of the nose and on the lobe of the ear. Deep sloughs appeared over the sacrum, heels, trochanter major, and nose sloughed off. The patient died thirty-eight days after admission to hospital, and was in coma a short period before her death. She drank of a liter of wine daily for years.

A partial postmortem examination was carried out. The femoral arteries were not occluded, and the caliber was appeared normal. The small arterioles in the extremities were obliterated by endarteritis. This obliterative process was intimal. Marked intimal proliferation was also noted in the kidneys and ovaries. A diagnosis of Buerger's disease was not made on the pulsations of the periphery.

It is impossible to determine the nature of the disease but it certainly was not Buerger's disease.

#### CASES OBSERVED AT THE MAYO CL

CASE 8—A woman, aged 44, of Norwegian parentage, born April 8, 1925, because of pain in the left foot of two years' duration. She first observed sharp pain in the sole of the foot, which was relieved by rest but at times was worse with exercise. This intermittent type of pain became localized in the third and fourth toes, they became numb and developed on the fourth toe, and it was amputated on May 29, 1924. Two weeks later the patient resumed her usual duties and felt well. There was no evidence of superficial phlebitis. Three weeks prior to admission to the clinic, the left toe and base of the first toe ulcerated and caused pain sufficient to disturb sleep. Pain when at rest was present at the time of admission. She was married twenty-five years and had three children who were living and well, but had had three self-induced abortions. Her health had been good. She had used tea and coffee to excess and had used alcohol moderately.

The patient was 63 inches (160 cm) in height and weighed 109 pounds (49.4 Kg). General examination was negative except for the condition of the extremities. Small ulcers (fig. 1) were present on the tip of the third toe and at the base of the first toe of the left foot. The fourth toe had been amputated. Arterial pulsations were normal in the right lower extremity, and in the left femoral and left popliteal arteries, but pulsations could not be felt in the left foot. Pulsations in the left leg and foot could not be elicited with the oscillometer. When the feet were elevated, there was pallor, graded 1, of the right toes, and pallor, graded 3, of the left toes. With the feet hanging in the dependent position, rubor graded 2 was observed in the first and third left toes in one and a half minutes. Definite rubor was not observed in the right foot. Observations were not made regarding pulsations in the arteries of the upper extremities. Roentgenograms of the feet and legs were negative for the presence of calcified vessels. The blood pressure, in millimeters of mercury, was 130 systolic and 75 diastolic. Repeated examinations of the urine gave negative results. The concentration of hemoglobin (Dare) was 70 per cent, and the acid hematin was 13.3 Gm for each 100 cc of blood. The erythrocytes numbered 4,230,000, and the leukocytes 6,900 in each cubic millimeter of blood. The concentration of urea was 34 mg, creatinine, 1.3 mg, and uric acid, 3.5 mg in each 100 cc of blood. The whole blood fibrin was 278 mg, and the plasma fibrin, 420 mg in each 100 cc of blood. The return of phenolsulphonphthalein in the urine was 60 per cent in two hours. The Wassermann reaction of the blood was negative.

CASE 5 (1. 1927) had severe aching months. The finger ached severely, and with symptoms, dry gangrene developed. The pain during the following had worked in a day.

The heart was normal. Pulsations were absent. A slight pulse could be felt. Sensation in the foot died shortly after the vessels were not

This is an example of angitis obliterans explaining many of

the left foot eliminated 0.44 calories per minute per square. One week later, the left foot eliminated 0.72 calories per square, which indicated a definite increase in the flow of blood. Rest in bed with radiant heat applied from eight to twelve exercises and contrast baths. Marked relief from pain followed the injection of radium chloride on two occasions. The first injection the second 25 micrograms. The patient was under observation and was free from pain when dismissed from the clinic.

nt received on May 7, 1927, stated that the amputation was in 1926, the left foot felt cold, and she was having pain. Written in April, 1928, stated that she was having the

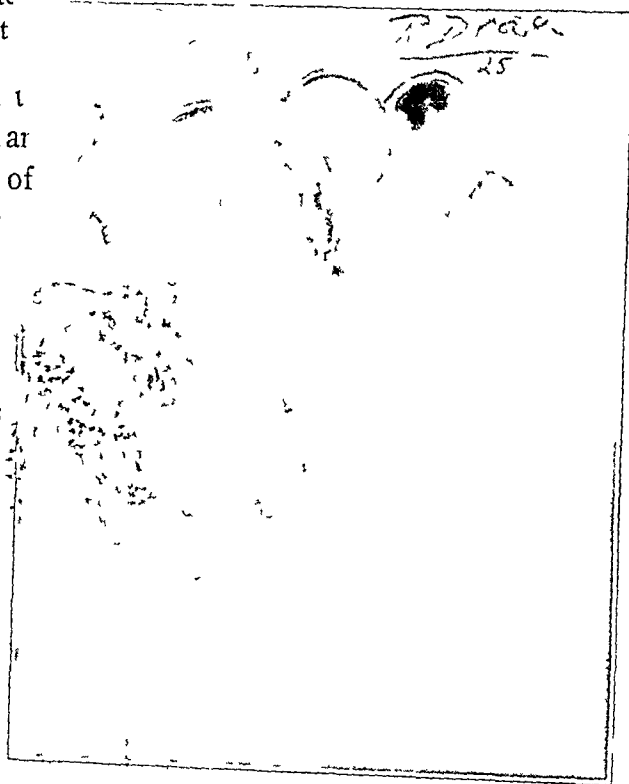


Fig 1 (case 8) —The appearance of the left foot. Ulcers are present at the base of the first toe and tip of the third toe, the fifth toe had been amputated.

same symptoms in the right foot, and that the right toes were sore. A letter written in September, 1928, stated that the patient had been in bed for six weeks with pain in both feet and gangrene in one toe. It has been impossible to obtain additional follow-up information in this case.

This case represents the first one of thrombo-angitis obliterans observed in a woman at the Mayo Clinic. Unfortunately, the data are not adequate to establish a definite diagnosis. There is no doubt of the fact that the patient had occlusive vascular disease of the lower extremities with severe pain, trophic changes and gangrene, which necessitated the amputation of two toes. In the absence of demonstrable sclerosis in the peripheral arteries and the clinical course of the disease, it seems highly probable that the occlusive vascular process

A high-contrast, black and white photograph of a dense, textured surface, possibly a rock face or a wall, with a diagonal line running across it. The texture is very rough and granular. The diagonal line is prominent, running from the upper left towards the lower right. There are some faint, illegible markings or text visible in the upper left corner of the image.

...the ... This h ... become  
... and ... mild cyanosis and  
... in height, a

ation was negative except All of the usual palps Scleroderma

The patient was again admitted to the clinic on April 21, 1932, because of superficial phlebitis of the left leg, which had failed to respond to medical treatment at home. Two large areas of superficial phlebitis, involving the upper third of the left leg, were present. Under local anesthesia, these areas were completely resected.

appearances of the vessel microscopic appearance of the vessels revealed a chronic thrombo-angiitis obliterans involving intima walls of the veins, with round cell infiltration and cells in the occluded lumens. Pulsations

CASE 11.—A Jewish woman, aged 60, was admitted to the clinic on Feb 25, 1929, and was discharged on April 10. She was again admitted on May 16, and remained in the hospital until March 1, 1930. Prior to her admission she was under observation in a hospital elsewhere for four weeks, where a diagnosis of thrombo-angiitis obliterans of the right leg was made. At the time of her first admission the disease of the right leg had been present for approximately six weeks. She did not speak English, and a history of the case was obtained from an interpreter. Approximately five or six weeks prior to admission the patient was confined to bed for a period of three days with tonsillitis. When she had been convalescing from this condition, she was suddenly seized with a sharp pain in the right foot. The toes became white, numb and painful. Later they became cyanotic. The pain was most marked in the sole of the foot. This pain was still present when she was admitted to the clinic. In the last two years she had had small subcutaneous nodules on both legs, which seemed to appear for a few days and reappear later in an adjacent area. It could not be determined whether these represented areas of superficial phlebitis, but probably they did, in view of the fact that acute superficial phlebitis developed along the inner aspect of the right leg and foot three days after admission. There was no history of intermittent claudication. She had never used tobacco in any form.

General examination was essentially negative except for the condition of the extremities. All of the palpable arteries in the upper extremities pulsated normally, as did both femoral arteries. Definite pulsations could not be felt in the right popliteal, right dorsalis pedis and right posterior tibial arteries. Good pulsations could be felt in the same arteries in the left leg. Ulcers were not present. The right leg was swollen and edematous, graded 1 to 2. The circulation seemed normal in the left leg. When the right leg was elevated, there was blanching, graded 1, and rubor, graded 1 to 2, with the foot in the dependent position. The foot felt cold. Readings of blood pressure taken daily showed a range of from 100 to 136 systolic and from 50 to 80 diastolic. The average readings were 120 systolic and 76 diastolic. Repeated examinations of the urine gave negative results. The concentration of hemoglobin (Dare) was 75 per cent, the erythrocytes numbered 4,600,000, and the leukocytes, 11,500. The differential count was normal. The acid hematin was 12.9 Gm for each 100 cc of blood. The urea was 14 mg and the sugar 89 mg in each 100 cc of blood. The Wassermann reaction of the blood was negative. Roentgenograms of the right foot and leg were negative for calcified vessels, but showed slight atrophy of bone with slight hypertrophic changes of the tarsal bones, and spurs on the calcaneum. Roentgenograms of the pelvis were negative. The ocular fundi were reported normal.

Three days after admission migrating thrombophlebitis developed which in a period of four weeks extended along the great saphenous vein from below the right knee to the groin. Approximately forty-eight hours after the phlebitis first appeared, a specimen was obtained for biopsy from the acutely thrombosed vein. Numerous cultures of the resected vein did not reveal a growth of organisms. The microscopic appearance of the vein was the same as that which we have seen from numerous veins obtained in a similar manner from known cases of thrombo-angiitis obliterans in men (fig 2). The edema of the foot and leg, which was present on admission, disappeared in three or four days but reappeared about four

weeks later, with symptoms that indicated deep thrombophlebitis of the right thigh. By April 10, clinical evidence of the thrombophlebitis had disappeared. The foot felt warm, the cutaneous temperature was normal. When the patient was dismissed from observation she was free from pain and remained so until three or four days prior to her second admission, on May 16, when she then had severe pain in the right foot. The right femoral artery still pulsated normally but no pulse could not be felt in the remainder of the extremity. Pulsations in the other lower extremity were normal. When the right foot was elevated there was no relief,

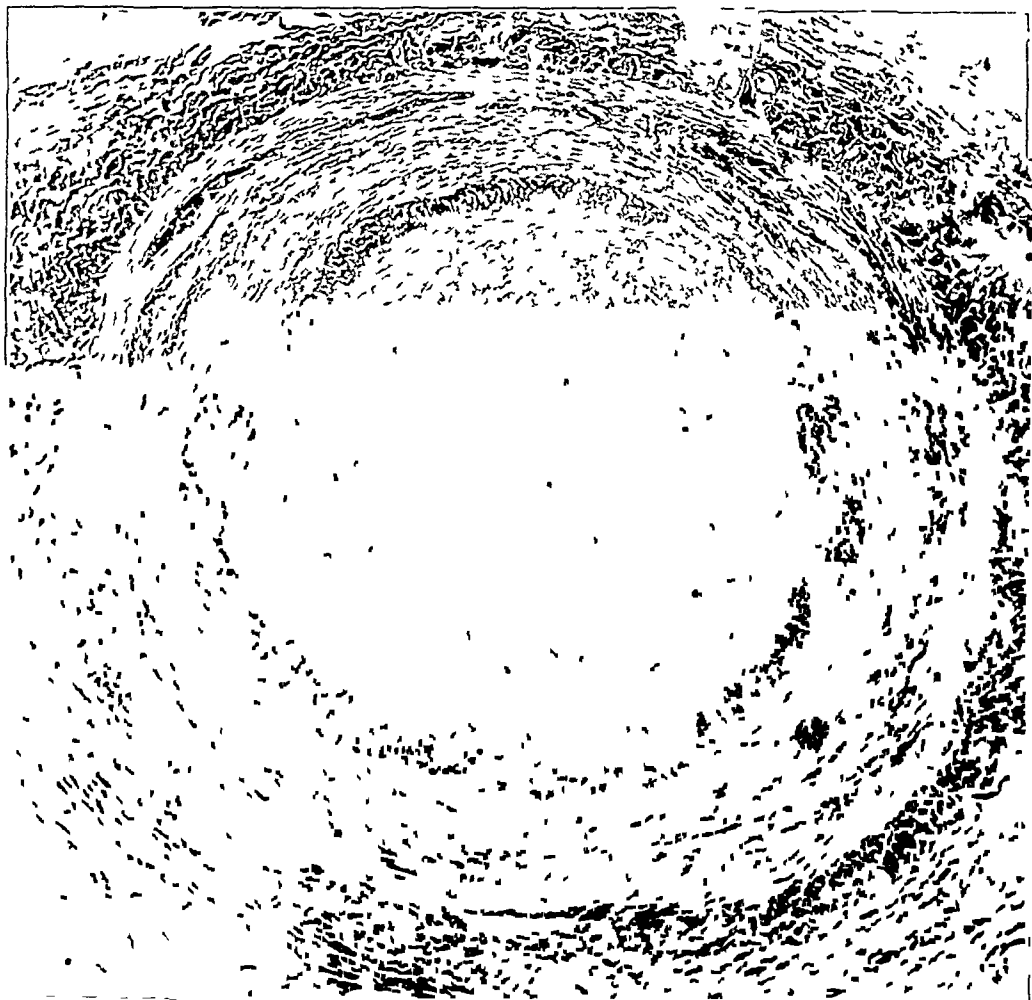


Fig. 2—Cross-section of a small superficial vein obtained at biopsy. The lumen is occluded with a cellular thrombus, and a chronic inflammatory reaction involves the wall of the vessel. Hematoxylin and eosin stain,  $\times 40$ .

graded 3, with rubor and cyanosis, graded 3 to 4, with the foot in the dependent position. Edema was not present, and the results of the remainder of the general examination were the same as on the first examination.

The use of typhoid vaccine and the usual medical measures failed to relieve the pain and on May 23 it was necessary to amputate the right leg at the juncture of the lower and middle third of the thigh. The condition did not improve following the operation. There was gradual thrombosis of the right femoral artery, and the stump failed to heal. The patient gradually failed, and died with terminal

breast carcinoma on June 28. Necropsy was not obtained, but the microscopic appearance of the vessels from the right leg showed the picture characteristic of thromboangiitis obliterans (Figs. 4 and 5).

CASE 11—A Jewess, age 22, first registered at the clinic on May 24, 1929, complaining of a "drowsy numbness" in both feet, which came on only after exertion, and which had been present since January 1. She also complained of "twinging pain" in the feet which came only at night when she was in bed, this began about March 1. She had considered herself in good health until the onset of her present illness. She was married and had one child, aged 19 months. There was no history of miscarriage. Her husband was living and in good health. When walking on January 1, the patient first experienced a tired feeling in the calf muscles of both legs, which, however, was not sufficient to cause her to stop walking. Since that time she had always had a drawing sensation or pain in the calves of both legs after walking four or five blocks. Complete relief had been obtained either from standing or from sitting for a minute or two, with

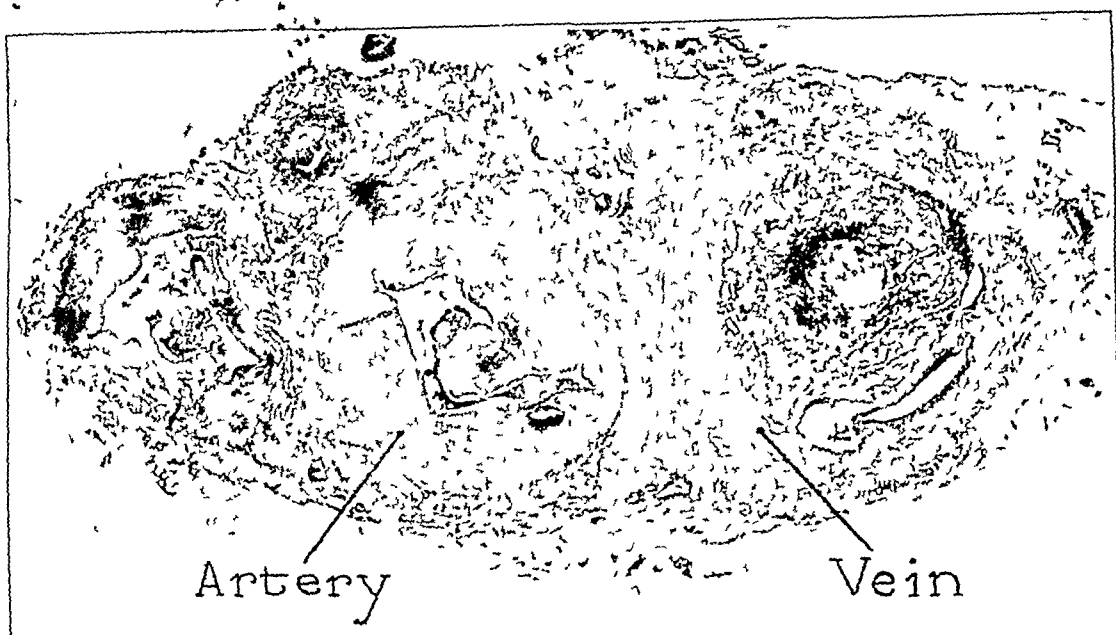


Fig. 3—Cross-section of the posterior tibial artery and vein. The larger vein is occluded by a chronic thrombus, and the artery is partially occluded by an organized thrombus. The artery and vein are closely bound together by a chronic inflammatory process. Hematoxylin and eosin stain,  $\times 15$ .

recurrence of the pain after she again walked a stated distance. She had never had this pain except after walking and it had been symmetrical. At the time of admission, she could walk only one block without pain in the legs. About March 1, she began taking capsules for this pain (intermittent claudication), and following this, at night, she frequently had twitching and a numb sensation in the toes of both feet, especially of the right foot. Occasionally she experienced a sensation of heat in the toes. She had discontinued taking the capsules three weeks prior to admission to the clinic.

General examination revealed a well developed and well nourished woman whose height was 64 inches (162.6 cm) and weight 120 pounds (54.4 Kg). Neurologic examination gave negative results. The blood pressure in the upper extremities ranged from 110 to 136 systolic and from 70 to 80 diastolic. We were unable to obtain blood pressure readings in the lower extremities. The pulsations in the



right brachial artery were almost normal, graded 3, and those of the left brachial artery were normal. The pulsations of the right and left radial arteries and of the right and left ulnar arteries were almost normal. The abdominal aorta was normal. Pulsations of the right femoral artery were normal, but the right

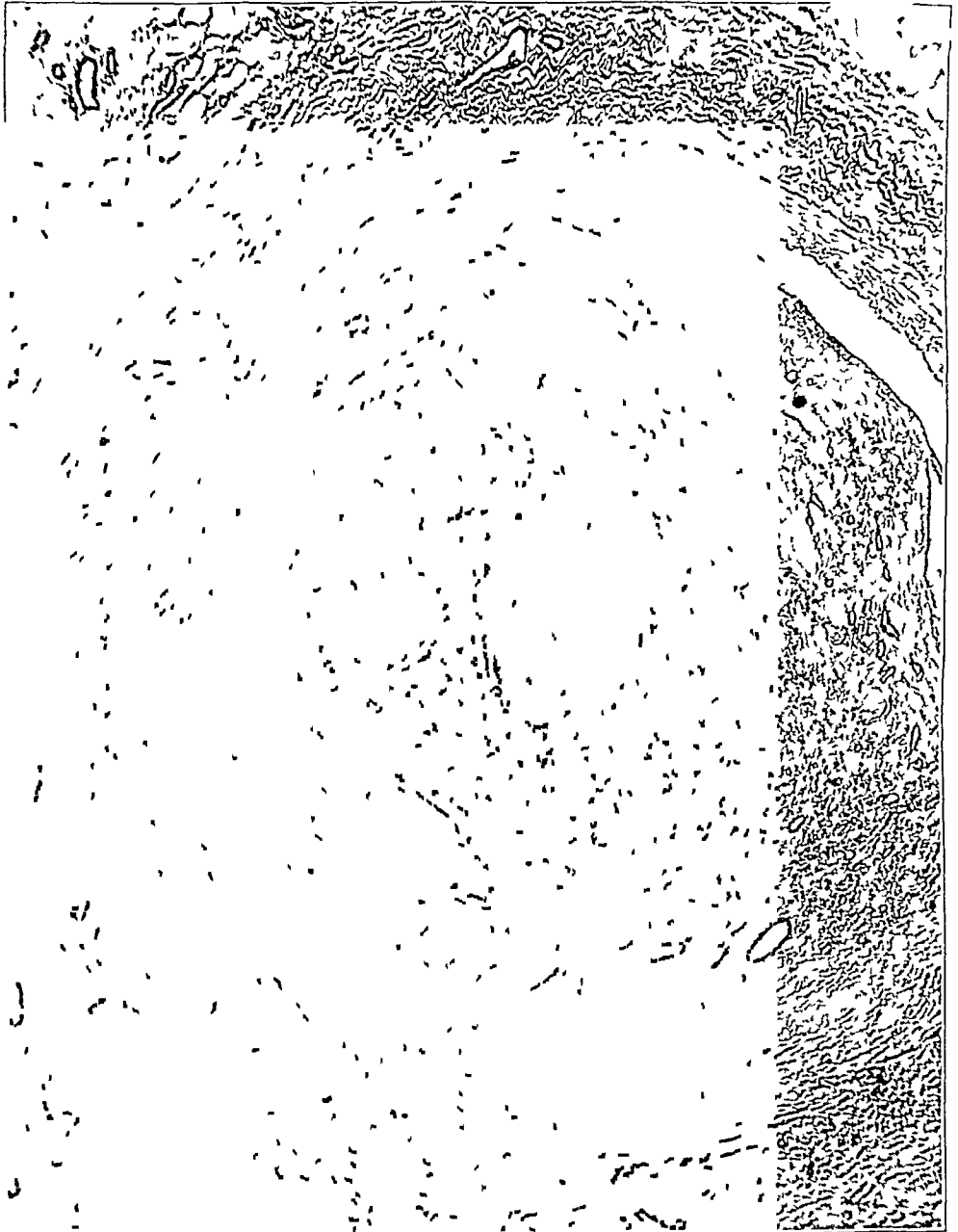


Fig 4—Cross-section of the posterior tibial vein, which is a high power view of the vein in figure 3. The chronic nature of the occlusive process and the attempt at canalization may be observed. Hematoxylin and eosin stain,  $\times 50$ .

popliteal, right posterior tibial and right dorsalis pedis arteries. Pulsations of the left femoral artery were approximately normal, those of the left popliteal, fairly normal, and those of the left posterior tibial and left dorsalis pedis, slight (fig 6a). With the feet elevated, there was marked blanching at 180 F, the feet assuming

ad , earance, and with the feet in the dependent position, there was  
 or, , of the toes

Exa tions of the urine were negative except for the presence of small  
 amo , lead. Of specimen of 600 cc of urine contained 0.14 mg of lead, a  
 sec , men of 500 cc contained 0.21 mg, and a third specimen of 600 cc  
 of 0.07 mg. Arsenic was not found in the urine. The concentration of  
 Hb, from (Dare) was from 70 to 75 per cent, the erythrocytes numbered  
 4,800,000, and the leukocytes, 9,400. The differential count showed the following  
 percentages: lymphocytes, 31, large mononuclears, 1, transitionals, 1, and neutro-  
 phils, 67. The platelets numbered 224,000, and the bleeding time was three and a



Fig 5—A high power view of figure 2, giant cell formation may be noted  
 Hematoxylin and eosin stain,  $\times 300$

half minutes. The coagulation time (Lee) was ten and a half minutes. The acid  
 hematin was 13.9 Gm for each 100 cc of blood. There was no basophilic stippling  
 of the erythrocytes, and no lead line around the gums. The Wassermann reaction  
 of the blood was negative. Roentgenograms of the thorax and teeth were negative.  
 The tonsils had been removed elsewhere when the patient was 8 years of age.  
 Foci of infection were not found. Examination of the ocular fundi was negative,  
 except for compound myopic astigmatism. The vasomotor index of the right and  
 left foot was 0, whereas that of the left hand was 4.

Treatment was instituted with radiant heat, postural exercises, contrast baths  
 and intravenous injections of typhoid vaccine. Four injections were given, the

dosage ranging from 50,000,000 to 100,000,000 organisms, with good systemic reactions (the temperature by mouth ranging from 102 to 103 F) following each injection. The pain at night of which the patient complained at the time of admission entirely disappeared following the first injection of typhoid vaccine. Her ability to walk improved approximately 25 per cent during her twenty-two day stay in the hospital. A tentative diagnosis of thrombo-angitis obliterans was made at the time of dismissal.

The patient continued the treatment under the direction of her home physician until the time of her second admission to the clinic on Dec 31, 1929. During this interval she had an intravenous injection of typhoid vaccine (100,000,000 organisms) every ten days with good reactions each time. She could walk only one block at a moderate gait when claudication pain developed in both legs. She had

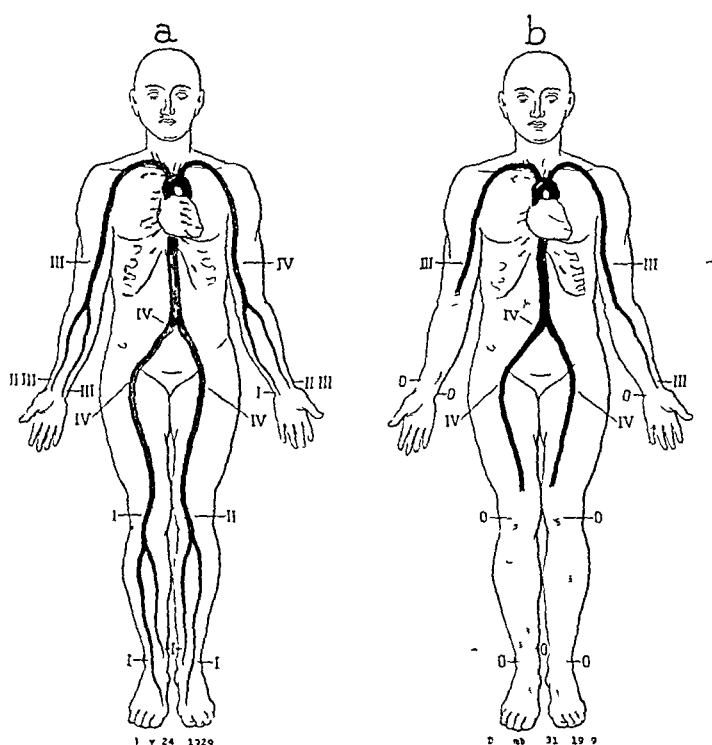


Fig 6—In *a* are shown the pulsations in the arteries at the time of the patient's examination on May 24, 1929, in *b*, the pulsations in the arteries at the time of the second examination here on December 31. *O* indicates the absence of pulsations, and *II* normal pulsations.

never used tobacco, and there was no history of superficial phlebitis. General examination was again essentially negative except for the condition of the extremities. The blood pressure in the upper extremities varied from 105 to 108 systolic and from 90 to 95 diastolic. Both brachial arteries were open, pulsations were almost normal, but none could be felt in the right radial and right and left ulnar arteries. Pulsations of the left radial artery were almost normal, and in the femoral arteries they were normal, but no pulsations could be felt in the lower extremities below this level except an occasional feeble pulsation in each popliteal space (fig 6*b*). Color changes were not noted in the hands when they were elevated and dependent, but when the feet were elevated, they were blanched, graded 3 to 4, with rubor, graded 2, of the toes in the dependent position. The

average temperature of the right hand at room temperature was 24 C (75.2 F), that of the left hand, 23.2 C (73.7 F), that of the right foot, 26 C (78.8 F), and that of the left foot, 25 C (77 F). The vasomotor index of the left foot was 19, of the right foot 29 and of the left hand 27. Examination of the urine was negative, and repeated examinations for lead were also negative. The concentration of hemoglobin (Dare) was 70 per cent, the erythrocytes numbered 4,840,000, and the leukocytes, 9,300. The concentration of urea was 21 mg in each 100 cc of blood, and the Wassermann reaction of the blood and a roentgenogram of the thorax were negative. The electrocardiogram disclosed a rate of 67, sinus arrhythmia, an inverted T wave in lead III, a diphasic P wave in lead III and notched Q-R-S complexes in lead III.

Bilateral lumbar sympathetic ganglionectomy was performed on Jan 8, 1930, at which time the second, third and fourth lumbar sympathetic ganglions and connecting rami were resected. Exploration of the gallbladder, stomach, kidneys and pelvis gave negative results. Convalescence was uneventful, and the wound healed by primary intention. The patient was up on the tenth day, and was dismissed from the hospital on the sixteenth day after the operation. Following the operation, the skin of the lower extremities was warm and dry, and the temperature was approximately the same in both lower extremities. Color changes were not observed on exposure to cold. The patient stated that the feet felt normal. She reported on April 8 that she was back at work teaching, and that she was able to walk two blocks without any definite discomfort in the legs.

The tentative diagnosis of thrombo-angiitis obliterans which we made in June, 1929, seems to have been definitely confirmed by the later developments in this case. Pulsations were present in all of the palpable arteries in the upper and lower extremities at the time of the patient's first examination, although they were definitely reduced in many of the vessels, as previously stated, but at the time of the second examination, approximately six months later, the pulsations had disappeared entirely from the right radial and right and left ulnar arteries, and all pulsations were practically absent below the femoral arteries in the lower extremities, yet there were no objective trophic cutaneous changes. The closure of the arteries demonstrates conclusively the presence of occlusive vascular disease, and not vasospastic disturbance of the vessels, such as obtains in Raynaud's disease. The absence of trophic changes in the skin indicates that the development of collateral circulation has kept pace with the occlusive process in the arteries. We do not know the significance of lead in the urine in this case.

CASE 12—A Russian Jewess, aged 47, came to the clinic on Aug 19, 1929, because of pain in the arch of the left foot, which had been present for three weeks. Ten months prior to admission she first began to have intermittent claudication pain in the arch of the right foot and calf of the right leg, which was sufficient to cause her to stop walking at the end of two or three blocks. Rest for a minute or two while standing gave prompt relief, it was not necessary to sit down in order to obtain relief. The pain recurred when she had walked a similar distance, followed by prompt relief with rest. There had been slow but gradual improvement in these symptoms since the time of onset. Three weeks prior to

admission the same type of pain developed in the arch of the left foot, associated with rest pain. She was unable to walk fifty steps without pain at the time of admission. During the past two years the left hand and arm had felt numb if she used them very much. This numb feeling was present only after exercise, and was relieved by rest. For the last two winters she had observed that the fourth and fifth fingers of the left hand turned white when exposed to cold. There was no history of superficial phlebitis. She had never used tobacco. She had been married for twenty-three years and had three children who were living and well. Her menstrual periods were still regular. She had consulted a physician two months prior to admission because of pain in the feet and legs, and the blood pressure at that time was found to be higher than normal.

The patient was 59 inches (150 cm) in height, and weighed 159 pounds (72 Kg). General examination was entirely negative, except for the presence of compensatory cardiac hypertrophy, graded 1, and the condition of the extremities. The right brachial, radial and ulnar arteries pulsated normally. The left brachial artery pulsated normally. Pulsations in the left radial artery were moderate, and pulsations in the left ulnar artery were intermittent, ranging from normal to a complete absence. Pulsations of both femoral arteries were almost normal, those of both popliteal arteries, fairly normal, and those of the right posterior tibial artery, almost normal, but pulsations could not be felt in the right dorsalis pedis artery, in the left dorsalis pedis artery or in the left posterior tibial artery. When the feet were elevated, blanching, graded 1, of the toes of the left foot was present, and rubor, graded 1, of the toes with the foot in the dependent position. Postural color changes were not observed in the right foot. The surface temperature of the right foot, determined by means of the electric thermocouple, was 25.1°C (77.1°F), and that of the left foot, 24.9°C (76.8°F).<sup>6</sup> The surface temperature of the hands was 33.9°C (93°F). The vasomotor index of the right foot was 4.3, of the left foot 1.8 and of the right hand 1.1. Repeated examinations of the urine gave negative results. The concentration of hemoglobin (Dare) was 80 per cent, the erythrocytes numbered 5,310,000, and the leukocytes, 8,900. The Wassermann reaction of the blood was negative. The concentration of urea was 28 mg in each 100 cc of blood. The return of phenolsulphonphthalein in the urine was 60 per cent in two hours. Roentgenograms of the feet and hands gave negative results, those of the legs showed evidence of a minimal amount of calcification of the vessels. Roentgenograms of the thorax gave negative results except for cardiac hypertrophy graded 1. Examination of the ocular fundi showed sclerosis, graded 2, of the retinal arteries of the so-called hypertension type. The blood pressure was 242 systolic and 136 diastolic. Blood pressure readings taken at hourly intervals over a period of twenty-four hours, with the patient moderately active during the waking hours, showed a range of from 170 to 230 systolic and from 110 to 140 diastolic. Similar readings obtained with the patient at rest, for a similar period, showed a range of from 160 to 215 systolic and from 80 to 140 diastolic. These observations indicated relatively severe benign hypertension. The electrocardiographic report did not indicate significant changes. The patient was placed on our usual hypertension regimen, with postural exercises, contrast baths and radiant heat for the lower extremities.

This patient had occlusive vascular disease involving the lower extremities and the left arm. Considering her age and the involvement of the upper extremities it is possible that the condition was of

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6 All surface temperatures were taken under controlled conditions, following rest and with the room temperature from 24 to 26°C (75.2 to 78.8°F).

the nature of thrombo-angitis obliterans, with superimposed arteriosclerosis. The intermittent pulsations in the left ulnar artery are suggestive of thrombo-angitis obliterans, as intermittent pulsations are frequently observed in this disease. Occlusion of the arteries in the upper extremities is rare in cases of simple arteriosclerosis. One cannot of course, be sure of the true nature of the occlusive process.

CASE 13—An unmarried woman, aged 28, of Scotch-Irish descent, came to the clinic on May 26, 1930, with a condition diagnosed as Raynaud's disease. Her history dated back over a period of sixteen years. At the age of 5 years, a condition diagnosed as tuberculous lymph nodes of the neck had developed. These were removed thirteen years later. It was not determined whether these represented tuberculous lymph nodes. At the age of 12 years, a crop of boils had appeared on both legs, and about the same time she first noticed cramplike pains in her feet and legs, which were thought to be rheumatic. In the last twelve years, she had continued to have attacks of superficial "abscesses" along both legs, at irregular intervals up to the time of her admission to the clinic. The cramplike pains, which probably were not the pains of intermittent claudication, continued, and two years prior to admission she finally resorted to the use of opium for relief from pain. She was a definite drug addict when admitted to the clinic. Eleven years prior to admission, severe pain developed in the right foot, which became blanching and cold. Gangrene of the toes followed, and auto-amputation of all the toes took place within a relatively short time. The following year a similar condition developed in the left foot with auto-amputation of the first and second toes. Secondary vasomotor disturbances with color changes had been present in the feet for at least eight or ten years. One year prior to admission, she had noticed coldness and cyanosis of the fingers of the left hand, especially noticeable on exposure to moderate degrees of cold. During the long course of her illness, talipes equinus of both feet had developed, the deformity being more marked in the right foot than in the left. There was no history of superficial phlebitis. She had smoked from fifteen to twenty cigarettes daily for a number of years.

General examination was essentially negative except for palpable lymph nodes in the inguinal regions and the condition of the extremities. The patient was well developed and well nourished, she weighed 137 pounds (62 Kg), and was approximately 64 inches (162.6 cm) in height. Examinations of the urine were entirely negative. The concentration of hemoglobin (Dare) was 70 per cent, the erythrocytes numbered 4,570,000, and the leukocytes, 7,400. The Wassermann reaction of the blood was negative. Roentgenograms of the thorax, the dorsal and lumbar vertebrae and the left forearm and hand were negative. Roentgenograms of the legs and feet disclosed marked atrophy and deformity of the bones of both feet. A biopsy specimen taken from the skin of the left leg showed scar tissue, slight obliterative changes in the vessels, loss of elastic tissue and small deposits of calcium. There was no evidence of tuberculoid structure, and the stain for the bacillus of tuberculosis was negative. Pulsations in the brachial arteries were almost normal, in the radial arteries they were fairly normal, in the right ulnar, they were almost normal, and in the left ulnar, they were absent. Pulsations in both femoral arteries were almost normal, and pulsations could not be detected in the lower extremities below this level. When the feet were elevated, there was pallor, graded 3, of both feet, and with the feet in a dependent position, there was rubor, graded 3. The veins in both feet filled relatively slowly after the feet were placed in a dependent position, indicating a poor flow of blood to the lower extremities. Neurologic examination was objectively negative. The vasomotor

index, which was determined after the intravenous injection of typhoid vaccine, was found to be 26 in the right foot, 31 in the left foot, 71 in the right hand and 87 in the left hand

Because of the marked occlusive vascular disease in the lower extremities and the relatively satisfactory vasomotor indexes, bilateral lumbar sympathetic ganglionectomy was advised. The operation was performed on June 3, 1930. The abdominal vessels appeared to be normal, and complete exploration of the abdominal cavity gave negative results. The patient recovered uneventfully from the operation. Because of vascular insufficiency which was developing in the hands and upper extremities, right and left cervical thoracic ganglionectomy and resection of the trunk were carried out on July 11. At the same time, an attempt was made to correct the deformity of the feet by lengthening the left Achilles tendon and removing a wedge of bone from the anterior outer part of the ankle, which consisted of the head of the astragalus and part of the neck and some of the tarsal bones. A plaster-of-paris cast was applied. Recovery was uneventful.

At the time of dismissal, on August 20, the patient was free from pain in the feet. She had had no recurrence of the lesions of the skin of the legs. A letter from the patient on March 31, 1932, indicated that the progress has not been satisfactory. Pain in the feet had returned, and she was again using morphine for relief.

CASE 14—A married woman, aged 38, of American extraction, registered at the clinic on Oct 10, 1930, with the chief complaint of pain in the feet, which had been present for approximately eleven months. She had smoked an average of twelve cigarettes a day for fifteen years, and had used alcohol to excess during this time. She had first noticed cyanosis of the left third toe in December, 1929, and about two or three weeks later, severe pain developed in this toe. A similar condition developed in the fourth toe about Jan 1, 1930, followed by pain and superficial gangrene. Both affected toes were incised and the bone scraped in February. Healing did not follow the operation, and severe pain continued in the left foot up to the time of admission to the clinic. There was no history of superficial phlebitis, and no definite history of intermittent claudication. The patient had lost approximately 20 pounds (9 Kg) during the course of her present illness, and had been unable to sleep for a greater portion of the time because of the severe pain in the foot. A diagnosis of Raynaud's disease had been made elsewhere.

General examination was negative, except for the condition of the extremities. Repeated examinations of the urine were negative except for slight traces of albumin. The concentration of hemoglobin (Dare) was 78 per cent, the erythrocytes numbered 4,350,000, and the leukocytes, 12,900, the differential count was normal. The concentration of urea was 18 mg in each 100 cc of blood. The return of phenolsulphonphthalein was 55 per cent in two hours. The serologic test for syphilis was negative. A fractional test meal showed a free hydrochloric acid of 20, and a total acidity of 38. The phosphorus of the blood was 4.2 mg, and the calcium, 9.1 mg. All of the peripheral arteries in the hands and feet pulsed normally, except the right dorsalis pedis artery, which was closed. When the feet were elevated, there was blanching, graded 3, of the right second, third and fourth toes, and graded 2 of the left fourth and fifth toes. With the feet in the dependent position, there was cyanosis, graded 1 to 2, of the left fourth and fifth toes. There were definite gangrene of the left fourth toe and definite trophic changes in the right second, third and fourth toes and the left fourth and fifth toes. Following an intravenous injection of typhoid vaccine, there was a definite rise in the surface temperature of the various toes. The left first toe showed a rise from 25.3 to

35.6 C (77.5 to 96 F) The rise in the right first toe was from 26.8 to 34.5 C (80.2 to 94.1 F), and the rise in the right third toe was from 24.8 to 32.6 C (76.6 to 90.6 F) The rise in the surface temperature of the left index finger was from 31.9 to 36.5 C (89.4 to 90.5 F) The temperature of the mouth rose only 0.6 C (1.09 F) The toes were more than 6 C (10.8 F) colder than the fingers

A definite rise in the surface temperature of the toes following injections of typhoid vaccine indicated that there was marked spasm in the collateral circulation, and for this reason, bilateral lumbar sympathetic ganglionectomy was performed on October 18 The second, third and fourth sympathetic ganglions were removed from each side Recovery from the operation was uneventful A definite line of demarcation developed in the left fifth toe, and it was finally amputated on November 18 Healing of the wound was delayed, but was complete on December 28

The postoperative records of the surface temperature of the feet three weeks following operation indicated that a maximal flow of blood to the feet followed bilateral lumbar sympathetic ganglionectomy On December 22, at normal room temperature, the surface temperature of the right foot ranged from 33.8 to 34.2 C (92.8 to 93.3 F), and that of the left foot, from 32.7 to 33 C (90.8 to 91.4 F)

Neurologic examination was objectively negative The blood pressure was 170 systolic and 110 diastolic at the time of admission Other blood pressure readings, taken twelve days after the bilateral sympathetic ganglionectomy, over a period of twenty-four hours, with the patient at rest, disclosed a range of from 165 to 185 systolic and from 95 to 120 diastolic Similar readings taken forty days after operation showed a range of from 155 to 210 systolic and from 90 to 125 diastolic

The results of microscopic examination of vessels from the amputated toe were suggestive of the same occlusive process which we have observed in men with thrombo-angitis obliterans (fig 7)

Repeated follow-up letters on this case indicate that the occlusive vascular process in the digits of the lower extremities is still progressive in spite of the bilateral lumbar sympathetic ganglionectomy Repeated attacks of superficial phlebitis have developed, with severe attacks of pain from time to time in both feet The pain at certain times resembled that observed in cases of primary erythromelalgia, because elevation of the feet seemed to give relief This, however, has not been a constant feature in the case The patient's last letter on March 30, 1932, indicated that the pain in the feet was decreasing, and she has been able to walk for a short time without much discomfort

CASE 15—A married woman, aged 38, of American extraction, registered at the clinic on Feb 24, 1931, her chief complaint being numbness and blanching of the fingers, which had been present since childhood, but had become definitely worse two years prior to admission, and the blanching, cyanosis and rubor which originally involved only the tips of the digits had extended back to the first and second joints in both hands Pain was not associated with the color changes, and trophic changes had not occurred in the skin or subcutaneous tissues This three-phase color reaction in the hands was precipitated chiefly by exposure to cold, although in the last year she had had a few attacks during the warm weather There was no history of superficial phlebitis or intermittent claudication



General examination was essentially negative except for the condition of the extremities. The hands appeared normal when examined in a warm room. Both radial arteries pulsated normally, but pulsation could not be detected in the ulnar arteries. The pulsations in the lower extremities were normal, except the dorsalis pedis arteries, which were reduced approximately 30 per cent. Even after the hands were immersed in hot water for a considerable period, pulsations could not be detected in the ulnar arteries. The hands were later immersed in cold water at 15 C (59 F) for a period of fifteen minutes, and the recovery phase of the various

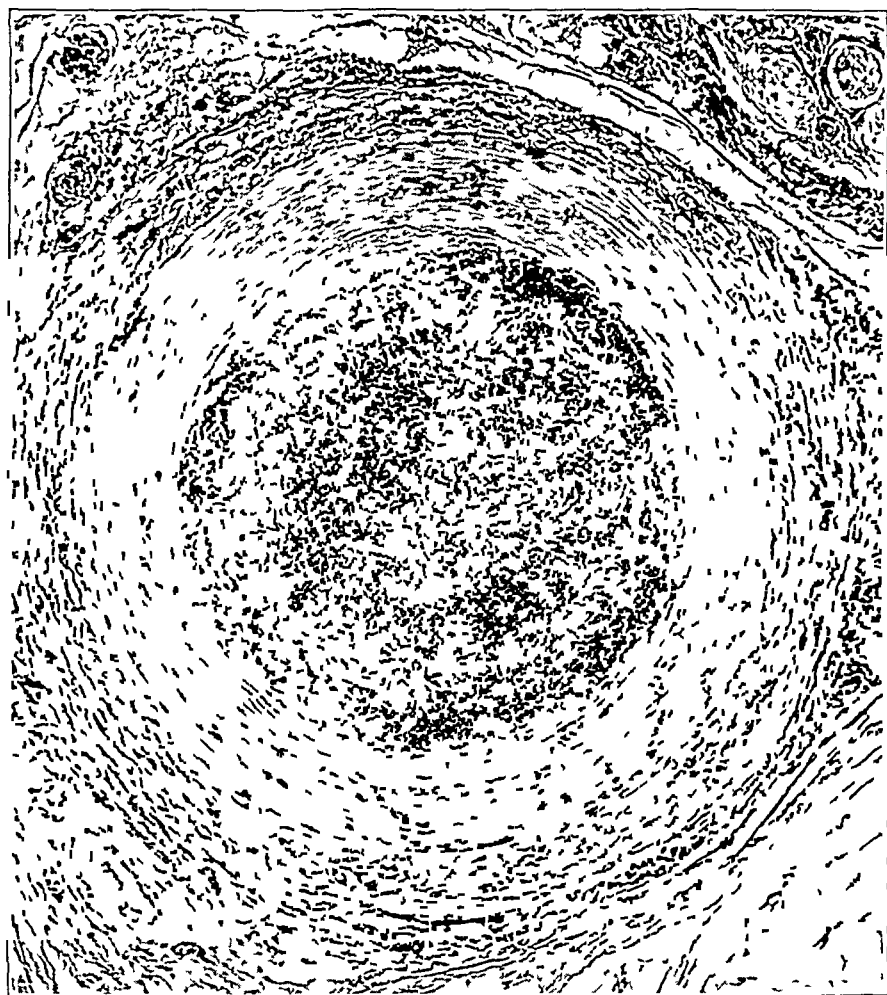


Fig 7—Cross-section of a small artery from an amputated toe. The lumen is occluded by an acute thrombus. Hematoxylin and eosin stain,  $\times 85$ .

fingers was determined separately. Spasm in the vessels could not be induced by this procedure, but there was a decided difference in the recovery of the end of the digits in the right and left hands. The left hand was 2 C (36 F) warmer than the right. The blood pressure was 135 systolic and 80 diastolic. Examination of the urine was negative. The hemoglobin was 14.4 Gm for each 100 cc of blood, the erythrocytes numbered 4,040,000, and the leukocytes, 5,500. The serologic test for syphilis was negative. Roentgenograms of the cervical vertebrae and thorax were negative.

The presence of occlusive vascular disease was conclusive, probably thrombo-angitis obliterans. Both ulnar arteries were definitely occluded, and this alone was sufficient to rule out Raynaud's disease. The asymmetry of involvement in the hands and the lack of uniform recovery in the digits when exposed to cold are further evidence of occlusive vascular disease.

CASE 16—An unmarried woman, aged 30, of American extraction, registered at the clinic on Jan. 13, 1932, her chief complaint being daily intermittent pain in the right foot and leg, which had been present for about a year. The pain seemed to be of two distinct types. Almost every morning about 5:30 she had been awakened by cramplike pain in the right foot, associated with a marked blanching of the toes and distal half of the foot. She had obtained prompt relief by immersing the foot in warm water. She also complained of intermittent claudication which developed in the calf of the right leg at the end of about seven or eight blocks of walking. She always obtained prompt relief by resting. The time of the onset of pain varied considerably, depending on the weather. In warm weather she could walk approximately twice as far without discomfort as in cold weather. In the last four months she noted blanching and rubor in the left foot, but actual claudication pain had not developed at the time of her admission. The right foot had remained colder than the left foot for a period of three or four months. The fifth toe of the left foot had been amputated in 1929 because of an infected claw. Trophic changes had not developed in the lower extremities. The past history was irrelevant except that the patient had smoked twenty cigarettes daily for ten years. There was no history of superficial phlebitis.

Arterial pulsations in the upper extremities were normal. Both femoral arteries and both popliteal arteries pulsated normally, but pulsations could not be detected in the right posterior tibial and dorsalis pedis arteries. The left posterior tibial artery pulsated normally, but only faint pulsations could be detected in the left dorsalis pedis artery. When the feet were elevated 180 degrees, there was pallor of both feet, graded 3, rubor of the right foot, graded 4, and rubor of the distal half of the left foot, graded 1 to 2, were present at 0 degree. Rubor developed much quicker in the left foot than in the right one. At normal room temperature the surface temperature of the right foot varied from 23.6 to 23.7 C (74.4 to 74.6 F), and that of the left foot from 22.5 to 22.8 C (72.5 to 73 F). The vasomotor index in the right foot was 3.3, and that in the left foot, 5.2. The patient was given intravenous injections of 50,000,000 typhoid bacilli, at which time the vasomotor index was determined. There was a rise in the surface temperature of the right foot from 23.6 to 32.1 C (74.4 to 89.7 F), and in the left foot, from 22.5 to 31.7 C (72.5 to 89 F). The temperature of the mouth rose from 36.7 to 38.2 C (98 to 100.7 F). Arterial pulsations could not be detected in the right foot at the height of the systemic fever, and there were no alterations in the arterial pulsations in the left foot. These data indicate that the patient had organic occlusive vascular disease in the lower extremities, with a large element of spasm in the collateral circulation. Neurologic examination was objectively negative. The blood pressure was 100 systolic and 70 diastolic. The hemoglobin was 14.7 Gm for each 100 cc. The erythrocytes numbered 5,180,000, and the leukocytes, 12,000. The differential count was normal, and the serologic test for syphilis was negative. Roentgenograms of the thorax, right tibia and fibula and the right foot were negative. Examination of the urine for lead and arsenic gave negative results.

A diagnosis was made of thrombo-angitis obliterans. Because of the patient's age, the relatively small amount of arterial occlusion in the right foot and the high vasomotor indexes, bilateral lumbar sympathetic ganglionectomy was advised, and this was carried out on January 29. Recovery was uneventful.

This represents an unusually interesting case of thrombo-angitis obliterans. In considering the relatively mild course which this disease runs in women, we think that the prognosis should be good for the preservation of the extremities. We do not think that there could be any doubt regarding the diagnosis in this case.

CASE 17—A married woman, aged 39, of English and Dutch extraction, first registered at the clinic on May 25, 1928. For a few years she had noticed gradually increasing nervousness, irritability and symptoms which were interpreted by the examining physician as indicative of nervous exhaustion. Examination revealed a well developed and well nourished woman, 64 inches (162.6 cm) in height, who weighed 140 pounds (63.5 Kg). A small adenoma of the thyroid gland was present. The blood pressure was 118 systolic and 80 diastolic. Examination of the urine was entirely negative. The concentration of hemoglobin (Dare) was 70 per cent, the erythrocytes numbered 4,210,000, and the leukocytes, 6,500. The serologic test for syphilis was negative. A roentgenogram of the teeth was negative.

The patient was again admitted to the clinic in an emergency on Feb. 22, 1932. Her past history was irrelevant except that she had smoked from fifteen to eighteen cigarettes daily for a period of fifteen years. She had had no recent infections or illnesses of any type. She had felt perfectly well until 3 a. m. of Feb. 15, 1932, at which time she was awakened by pain in the right hand and forearm. The pain was excruciating. The hand and forearm appeared blanched, cadaveric and devoid of blood. About ten hours later the extremity had splotchy red areas, and in the course of two or three days these became bluish black. The extremity was cold and felt numb. She was unable to move the fingers of that hand. The pain continued and seemed to be of a burning character. Heat was applied in order to increase the flow of blood to the hand and forearm, but this did not serve to eradicate the pain.

General examination was again essentially negative except for the condition of the extremities. The right hand was cadaveric and felt cold, and there was first-stage gangrene of the tips of the thumb and the third, fourth and fifth fingers. Only faint pulsations could be felt in the right brachial artery. Pulsations were entirely absent in the right radial and ulnar arteries. Pulsations were also absent in the left posterior tibial and left dorsalis pedis arteries. All of the other peripheral arteries pulsated normally. The gangrene in the thumb and the third, fourth and fifth fingers gradually extended to approximately the first joint, and definite lines of demarcation developed in the course of four weeks. These gangrenous digits were amputated on March 21, and the patient was dismissed on March 30. The stumps had shown only a slight tendency to heal following the amputations, but there seemed to be a slow although definite increase in flow of blood to the right hand. We believed that the wounds would eventually heal.

At the time of the patient's dismissal pain had practically disappeared. The blood pressure was 124 systolic and 86 diastolic. The heart appeared to be normal. The electrocardiogram showed a rate of 89, sinus arrhythmia, an inverted T wave in derivation III, notched P-waves in derivations I, II and III, an exaggerated P wave in derivation II and slurred Q-R-S complexes in derivations I, II and III.

Repeated examinations of the urine were negative. The hemoglobin was 12.7 Gm for each 100 cc, the erythrocytes numbered 4,200,000, and the leukocytes, 13,900. The concentration of urea was 18 mg in each 100 cc of blood. Roentgenograms of the thorax and right hand gave negative results. The surface temperature of the right hand at the time of dismissal ranged from 28.7 to 32.3 C (83.6 to 90.1 F), which indicated that a fairly adequate collateral circulation had been developed in the involved extremity. The history of sudden arterial occlusion in the right arm strongly suggested an embolic state, but we could find no source for an embolus and are inclined to believe that this patient had a sudden thrombosis, probably at the bifurcation of the brachial artery. The final diagnosis was thrombo-angitis obliterans.

The onset of sudden arterial occlusion in the right upper extremity, as in this case, is not unusual in cases of thrombo-angitis obliterans and has been observed rather frequently in our experience. Sudden closures of this type, which involve the popliteal arteries of persons of this age usually result in gangrene of the foot, and amputation at or above the knee is usually necessary. In this case only the distal joints of four digits were lost. We have never found it necessary to advise amputation of a hand or upper extremity as the result of thrombo-angitis obliterans.

#### COMMENT

The most perfect example of the incidence of disease as related to sex is hemophilia. Of the diseases that attack common structures of both sexes, probably those of the vascular system are most common among men. This is seen to some extent in diseases of the coronary arteries, and in arteriosclerosis of the peripheral vessels. In Raynaud's disease, the incidence is much higher among women. Our statistics show an incidence of 9 to 1, and this predominance is significant in the diagnosis of Raynaud's disease. Thrombo-angitis obliterans, which probably is an inflammatory disease of the arteries and veins due to some infectious or toxic agent, exhibits a similar percentage preponderance in favor of men. This difference in sex could be related to

1. Some focus of infection peculiar to men. This has called our attention to the possibility of the prostate gland or seminal vesicles as fulfilling this rôle. Our studies have shown that in about 60 per cent of cases of thrombo-angitis obliterans, prostatitis, graded 2 or more, has been present. No direct causal relationship could be proved between this focus and thrombo-angitis obliterans.

2. Some endocrine basis peculiar to the male sex which could play a dominant part in the causation of this disease. Proof has not been forthcoming.

3. Tobacco. Several workers (Silbert, Meyer, Weber and Erb) have insisted that tobacco is the etiologic basis of thrombo-angitis

obliterans Barker's<sup>7</sup> analysis of the use of tobacco by men in three hundred and fifty cases of thrombo-angitis obliterans has shown that 3 per cent have never used tobacco, and 20 per cent have used it in small quantities. He has also called attention to the fact that the disease apparently is more serious if tobacco is used freely. Meleney and Miller, Jablons,<sup>8</sup> Koyano and others have reported the cases of patients who were not smokers. If tobacco is an important factor, one would expect a changing incidence of thrombo-angitis obliterans among women with its increasing use by this sex. In this series of ten cases from the clinic, three patients (cases 13, 14 and 16) used tobacco.

4. There is a premise that women may have the disease in a much milder form, and that the disease is overlooked because of the failure of development of gangrene or the more serious sequelae.

Of the possible explanations, the most logical, in our opinion, is the fourth. In four of our cases the disease was severe enough to produce gangrene. In the remaining cases, the disease had been comparatively mild. These cases might have been easily overlooked if one were not definitely searching for evidence of the disease in the presence of this condition of the extremities. If more women patients were examined as a routine measure for pulsations in the peripheral arteries, the absence of pulsations in one or more vessels, without symptoms, would be found in a certain small percentage. Likewise, the incidence of superficial phlebitis is not rare among women. The question arises, do chronic relapsing forms of superficial phlebitis, which if it occurs among men we have no hesitancy in diagnosing as thrombo-angitis obliterans, justify this diagnosis of the condition among women? In a certain percentage of these cases of superficial phlebitis one or more arteries are closed (case 9). Unfortunately, our knowledge has not progressed to the point at which the pathologic changes in phlebitis can be accepted as pathognomonic of thrombo-angitis obliterans. The clinical course of the disease is probably more diagnostic than the pathologic picture. The total number of cases of thrombo-angitis obliterans which we have studied is slightly less than seven hundred. We found ten cases in which the patients were women. This is an incidence of approximately 1 to 70 (1.2 per cent). Bueiger reported two cases in women which were diagnosed clinically. Meleney reported one case in which the patient was a Chinese woman, the pathologic picture and clinical course were typical of the disease. Three of the patients in our series were of Jewish extraction. Their disease was

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7 Barker, N. W. The Tobacco Factor in Thrombo-Angitis Obliterans, *Proc. Staff Meet., Mayo Clin.* 6:65 (Feb. 4) 1931.

8 Jablons, Benjamin. Thrombo-Angitis Obliterans, *Internat. Clin.* 3:193 (Sept.) 1925.

more severe than in the seven Gentiles. A similar clinical impression was gained in our series of men, the disease of the Jewish patients seemed more serious and intense than that in the other races.

#### CONCLUSIONS AND SUMMARY

Further consideration of this disease, with its predilection for men, should be delayed until a larger number of women with complaints in the extremities have been examined. We are of the opinion that this disease has a higher incidence among women than is brought out by this study. The failure to recognize this is due probably to the facts that the disease is relatively mild among women and the diagnosis is overlooked. If this is a chronic infectious disease, as the work of Buerger<sup>9</sup> and of Horton and Dorsey<sup>10</sup> seems to indicate, no available explanation is at hand.

The ages in the ten cases reported here were 44, 43, 60, 71, 47, 28, 38, 38, 30 and 43, respectively. The average age was 39 years.

Four patients were treated by bilateral lumbar sympathetic ganglionectomy, one of these also had bilateral cervicothoracic sympathetic ganglionectomy. One patient had an amputation of the right leg, and the other patients were treated medically. The treatment, for the most part, has proved satisfactory. The disease among women apparently runs a similar, but definitely milder, course than among men.

The cases of ten women with thrombo-angitis obliterans observed in the Mayo Clinic are recorded, which represents, so far as we are aware, the first series among women to be placed on record.

<sup>9</sup> Buerger, Leo. Thrombo-Angitis Obliterans. Experimental Reproduction of Lesions, Arch Path **7** 381 (March) 1929.

<sup>10</sup> Horton, B. T., and Dorsey, A. H. E. Experimental Thrombo-Angitis Obliterans. Bacteriologic and Pathologic Studies, Arch Path **13** 910 (June) 1932.

# MITOTIC MYELOCYTES IN THE PERIPHERAL BLOOD IN A CASE OF MYELOID LEUKEMIA IN A NEGRO

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Indirect or mitotic cell division of nongranular leukoblasts occurs rather frequently in certain types or stages of leukemia. The presence of mitotic leukoblasts in the peripheral blood has been the subject of several recent reports (Dock, Tannhauser, Bowcock and Bishop, Groat, Rabinovici, Bowcock and Dickson) <sup>1</sup> Groat's case showed all stages of mitosis in the peripheral blood, from prophase through telephase to daughter cells, these cells were free from granules.

I am unable to find mention of the occurrence of granular mitotic myelocytes in the peripheral blood, except in the report of Dock. Hirschfeld <sup>2</sup> illustrated mitotic myelocytes in a bone marrow smear. One might question the ability of a cell as mature as a myelocyte to undergo mitotic division.

The following case is of interest because smears from the peripheral blood showed frequent examples of all stages of mitosis in cells containing neutrophilic granules. The case is of further interest because leukemia seems to be rare in our large service for Negroes. In the accompanying series of photomicrographs (figs 1 to 5), two mitotic erythroblasts from the same case are shown for contrast with the myelocytes.

## REPORT OF CASE

*History*—A Negro, aged 23, married, a laborer, was admitted to the Grady Hospital, Emory University Service, on April 28, 1932. The complaints were pains in the left leg and abdomen, weakness of the left leg, dizziness, headache and

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From the Grady Hospital, Emory University

1 Dock, George. Mitosis in Circulating Blood, *Physician & Surgeon* **26** 1 (Jan) 1904. Tannhauser, S. Ueber Mitosen im stromenden Blut bei einem Fall von akuter Leukämie, *Virchows Arch f path Anat* **264** 391, 1927. Bowcock, H, and Bishop, E L. A Case of Acute Leukemia with Unusual Cell Forms in the Blood, *Ann Int Med* **3** 1252 (June) 1930. Groat, W S. Mitosis in Myeloblasts in Peripheral Blood, *Am J M Sc* **180** 607 (Nov) 1930. Rabinovici, E. Ueber einen Fall von Mikromyeloblastenleukämie mit zahlreichen Mitosen im peripheren Blute, *Folia haemat* **43** 132, 1930. Bowcock, H, and Dickson, R W. Mitotic Leukoblasts in the Peripheral Blood of a Case of Acute Leukemia, *Ann Int Med* **4** 1344 (April) 1931.

2 Hirschfeld, H. *Lehrbuch der Blutkrankheiten*, Berlin, A. Hirschwald, 1918, plate 3, fig 38.

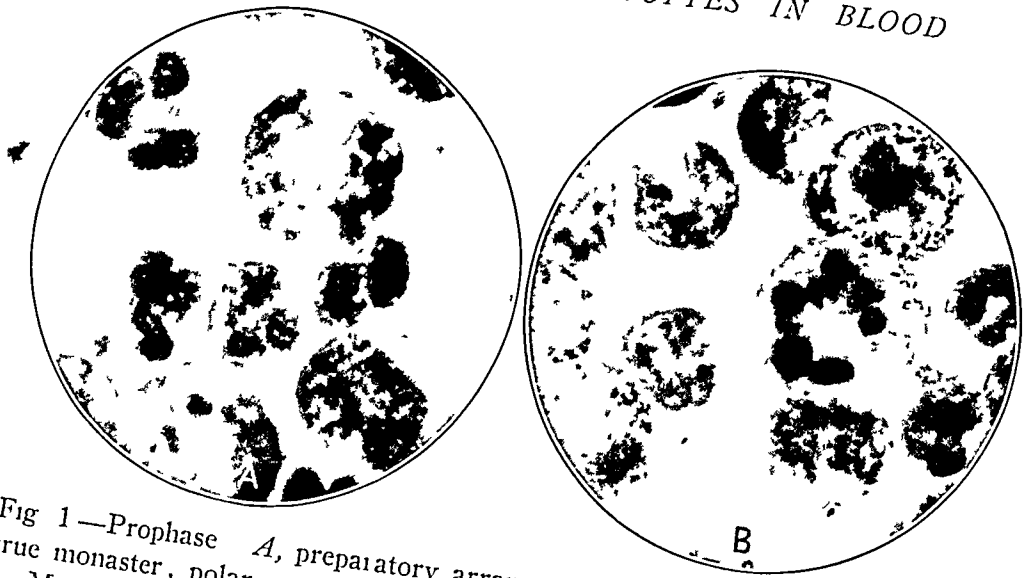


Fig 1—Prophase *A*, preparatory arrangement of chromatin into loose skein  
*B*, true monaster, polar view (?), closed skein with definite chromosome forma-  
tion Magnification,  $\times 1,100$

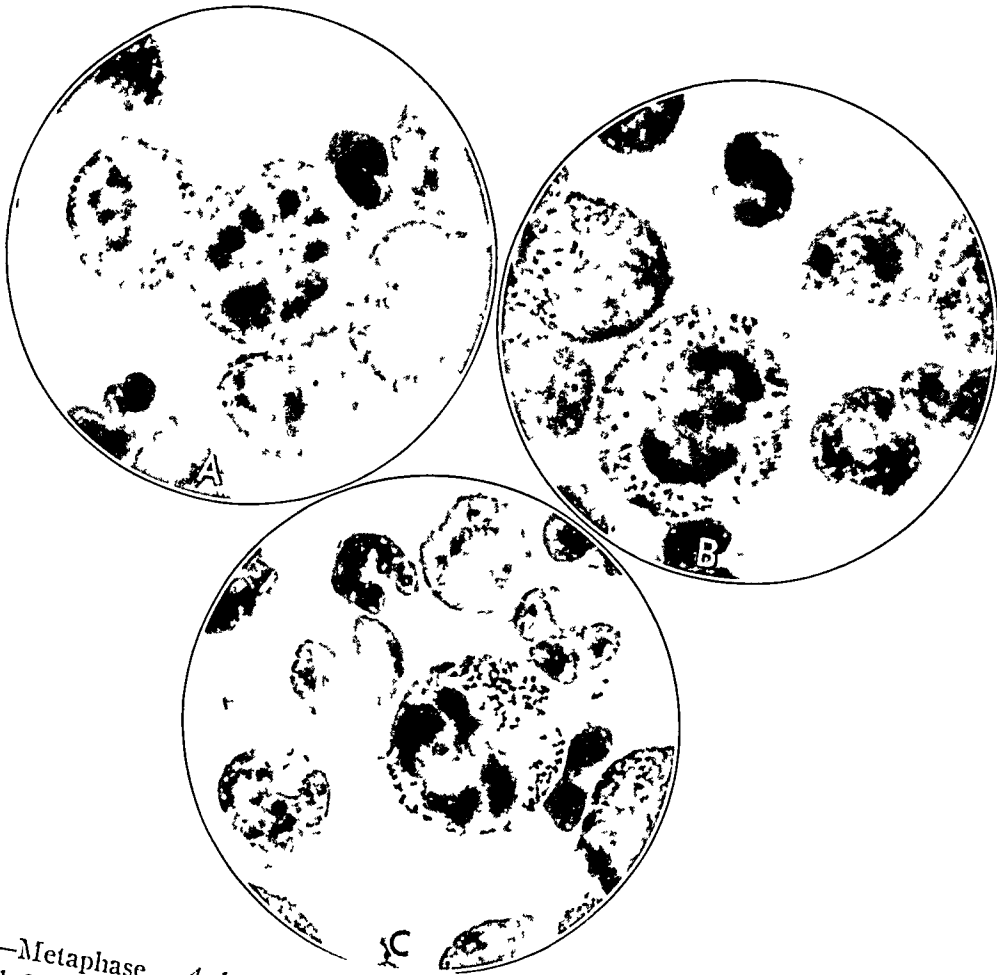


Fig 2—Metaphase *A*, beginning separation of chromosomes, polar view (?)  
*B* more definite separation of chromosomes with early diaster formation *C*,  
advanced separation of chromosomes to form a definite diaster Magnification,  
 $\times 1,100$



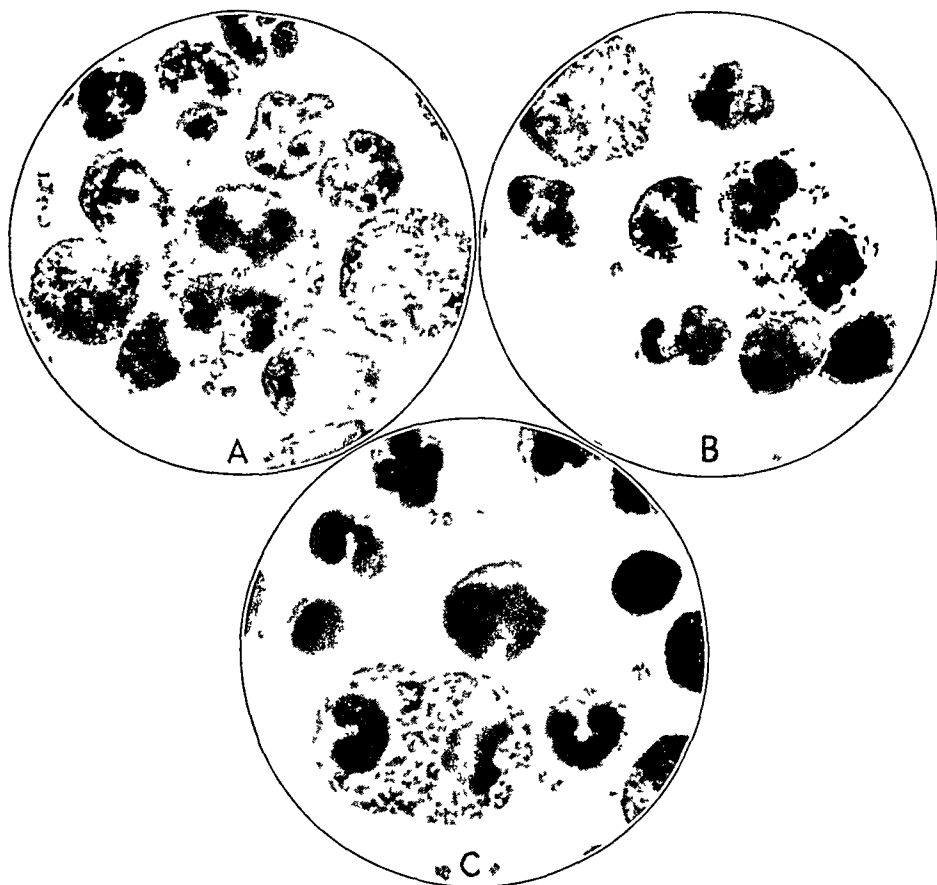


Fig 3—Anaphase *A*, early polar concentration with reassembling of chromosomes *B*, condensation of chromosomes and beginning separation of cell mass *C*, slightly later stage (note heavy granulation) Magnification,  $\times 1,100$

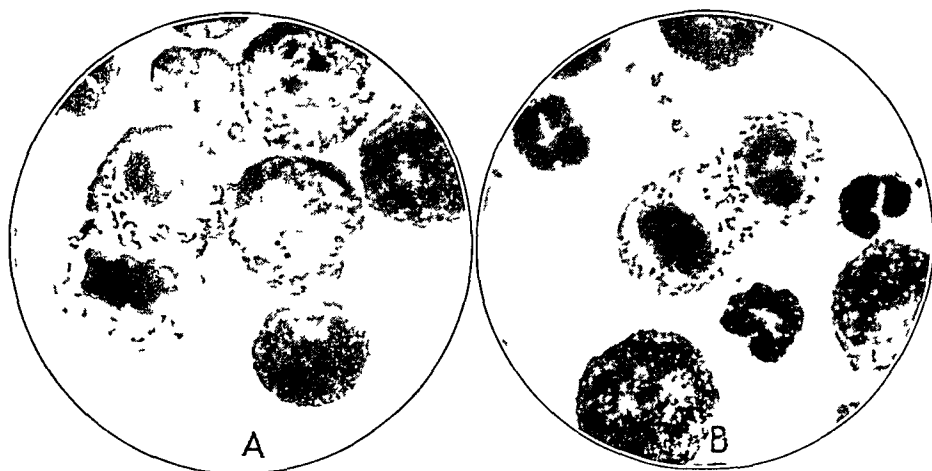


Fig 4—Telephase *A*, beginning equatorial constriction of cytoplasm *B*, advanced equatorial constriction of cytoplasm and disappearance of identity of individual chromosomes Magnification,  $\times 1,100$

general weakness. The present illness was said to have started with an injury to the left knee on April 1, 1931. The knee became greatly swollen, but improved sufficiently in five days for resumption of work. A few days later the patient became confined to his bed for a week with a febrile illness diagnosed as influenza. On resuming work he suffered from severe pain in the left groin and pains and weakness in both legs. After an examination of his blood he was given an intravenous injection. This was followed by headache, dizziness, abdominal cramping pains and the vomiting of a large amount of blood. Three days before admission to the hospital he noted a mass in the left side of the abdomen.

His mother had been operated on for cancer of the rectum. The remainder of the family history was unimportant. The patient was the only child. He had had the usual diseases of childhood. He had been confined to bed for seven weeks during 1922 with typhoid fever. He had had gonorrhea during 1924 and 1925 and smallpox during 1926. He had had a cough at intervals for two years, which occasionally produced blood-streaked sputum. During a year there had been an



Fig 5—Mitotic erythroblasts shown for contrast, with the mitotic leukoblasts in figures 1 to 4. Magnification,  $\times 1,100$

occasional drenching night sweat. For eight months there had been some shortness of breath on exertion. For four months he had vomited frequently immediately after eating. He had been married for six years. His wife was well, but there had been no pregnancies. His highest weight had been 180 pounds (81.8 Kg) during 1922, and his present weight was about 170 pounds (77.3 Kg). The remainder of the history was unimportant.

*Physical Examination*—The patient was well nourished and well developed and showed no evidence of discomfort. The temperature, pulse rate and respiratory rate were normal. The mucous membranes were pale. There was slight ulceration of the gums with a tendency to bleeding. The tonsils were large. There was enlargement of the superficial cervical, axillary, epitrochlear and inguinal glands. There was bulging of the left side of the abdomen, and in this area there was a palpable, freely movable mass extending from the left costal margin downward to slightly below the umbilicus and from the left flank medially to within 2 cm of the umbilicus, a notch could be felt, and pressure over the mass produced moderate pain. The edge of the liver was palpable 4 cm below the right costal

margin in the midclavicular line. There was a small umbilical hernia. A small abscess was found just above the left knee. The remainder of the findings were normal.

*Laboratory Examination*—A specimen of urine was normal. The Wassermann reaction of the blood was reported as anticomplementary. The red blood cells numbered 2,200,000 per cubic millimeter. The hemoglobin (Dare) was 50 per cent. The leukocytes numbered 670,000 per cubic millimeter. The blood platelet count was 400,000. In the stained blood smears (Wright's stain) the predominant abnormal cells were classified as neutrophilic myelocytes. Many nucleated red blood cells were present, some of these were seen in the stages of mitotic division. Myeloblasts were rare, an occasional example contained Auer bodies. Lymphocytes were seldom recognizable. Hemohistiocytes and megakaryocytes were seen rarely. The most striking point of interest in the stained smears was the frequent presence of typical stages of mitosis in granular myelocytes. All stages of mitosis were encountered, prophase, metaphase, anaphase and telophase. Eight or ten examples were sometimes encountered in one preparation. The cytoplasm of these mitotic cells appeared to be thin, it took a pale blue stain and often showed a faint ground-glass appearance. The nuclear material stained violet to purple. The cells contained varying numbers of fine and coarse neutrophilic (hilac) granules. Mitotic erythroblasts were much less frequently seen. The cytoplasm of the latter appeared to be thick to the periphery of the cells, it took a slate blue stain and often contained rather coarse dark blue granules. The nuclear material of the erythroblasts was deep bluish purple and had the appearance of being dense.

Roentgen examination of the chest showed a moderate increase in the shadows of the hilus gland. Roentgenograms of the long bones showed no abnormalities.

*Course*—The patient was seen at intervals during a period of three months. Two transfusions of 370 cc and 500 cc of whole blood produced some improvement of the anemia. Deep roentgen therapy was given seven times at the Albert Steiner Clinic, Grady Hospital. The leukocyte count decreased gradually to 134,000 per cubic millimeter at the last observation, the percentage of myelocytes was usually about 30. During the latter part of the treatment the incidence of mitotic myelocytes was greatly decreased. The patient has moved to a distant city, but is reported to be alive and in fair condition.

The photomicrographs were made by the Photographic Department, College of Medicine, Syracuse University.

# GRAPHIC REGISTRATION OF HEART SOUNDS BY THE ARGON GLOW TUBE

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Graphic representation of the auscultatory phenomena of the cardiovascular and respiratory systems, of value to clinician and teacher, has not been widely used because of technical difficulties. The apparatus commonly used has been suited to the physiologic laboratory and not to the office or clinic. The oscillographic records of Einthoven, Lewis, Fahr, Watson and Wemyss Williams, Wolferth and Hyman, and use of the capsule method by Frank, Wiggers, Broemser, A. Weber and others have thrown considerable light on the physical characteristics and mechanism of the sounds and made more accurate the time relations of heart murmurs. Students of graphic records develop the visual sense in their study of the timing and character of the auscultatory phenomena. They learn to form a visual image of the stethoscopic findings at the time of physical examination. The importance of the stethoscopic findings has recently been properly emphasized by Herrick<sup>1</sup>

## METHOD AND MATERIAL

A method of recording heart sounds, employing some of the newer principles of sound registration, is here briefly reported. In addition, a few representative clinical conditions will be discussed illustrating the sound curves obtained and their significance. The method adapts the argon glow tube to the ordinary electrocardiographic camera to record sound vibrations as light and dark bands simultaneously with the electrocardiogram. These bands are legible even when recorded at camera speeds of 25 or 50 mm per second. This method appears to answer the requirements of simplicity, low cost, ease of repair through the use of standard parts, constant time relations, superior faithfulness over a wide range of sound frequencies and adaptability to the present electrocardiographic machines. The apparatus is a combination of well tried units, developed by electrical manufacturers for other purposes and described in detail by them. In addition, it records a sound tract that permits later reproduction of the sounds from the film by means of the photo-electric cell. The lack of distortion has been proved by the reproduction of the tones.

A discussion of the microphone and amplifying devices is included, since they are the greatest factors in expense and satisfactory operation. The microphone must be free from distortion and of low threshold to detect the soft murmurs. It should record frequencies even lower than can be heard by the human ear. The

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From the Medical Clinic of the Peter Bent Brigham Hospital, Boston

<sup>1</sup> Herrick, J. B. In Defense of the Stethoscope, *Ann Int Med* 4 113 (Aug) 1930

condenser type of microphone,<sup>2</sup> attached to the stethoscope chest piece by a rubber tubing of such short length as to avoid resonant effects and time loss, has given good results, and by this arrangement the microphone is placed in the position of the ear in ordinary auscultation

Any efficient, valve-tube audio-frequency amplifier will give legible results, but it must be very sensitive to react to the low voltage from the microphone caused by the fainter sounds, and must be very stable to introduce no artefacts at low frequencies and during long pauses. The best results have come from well made, three-stage amplifiers of the resistance and large condenser, or battery-coupled types

The argon tube is caused to glow, i.e., to emit a visible electron stream of high photographic power, by passing through it 350 or more volts at 2 to 5 milliamperes, regulated by a variable 25,000 ohm resistor in series. The same battery supply may be used for the last tube of the amplifier and the glow tube. When the output of the amplifier is impressed on this circuit, remarkable variances in light intensity

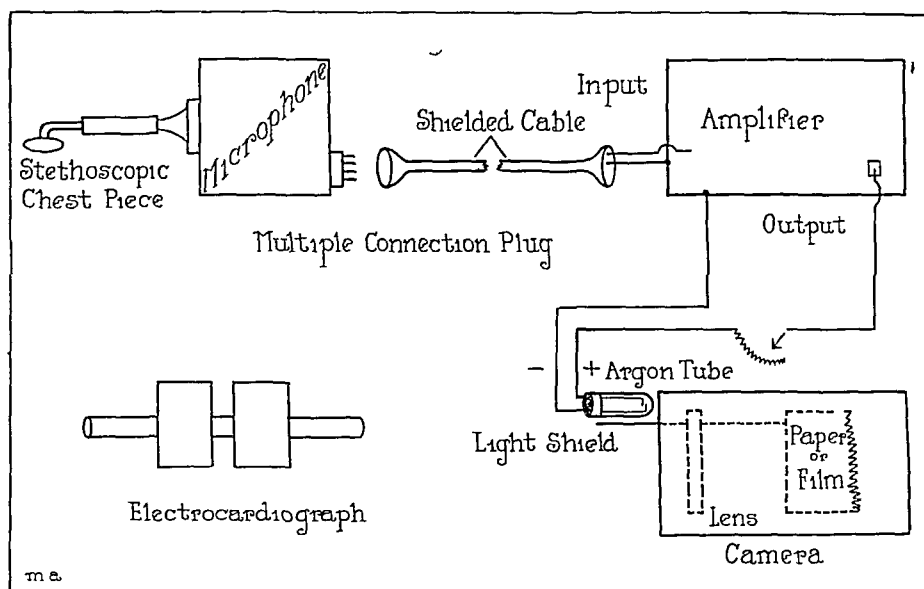


Fig 1—Schematic diagram showing apparatus for recording heart sounds

are produced without afterglow, even when operated at frequencies far above those used in these investigations. A positive current impulse from the amplifier causes a proportionate increase in the brilliancy of the glow and the negative impulse a proportionate decrease in brilliancy, the variations have sufficient photographic power to be registered plainly on moving bromide paper through a slit of 0.2 mm or less in width. A smaller glow tube, with a more concentrated streak of light, to operate on 250 or less volts and small enough to go inside many of the electrocardiographic camera cases is being tried.

The simplest installation for the present cameras has been to place the argon tube in front of and at one end of the camera slit and to isolate a sound tract from the remainder of the film by use of a thin lead sheet fitted to the inside of the

2 Equally good results, requiring less amplification and expense, may be had by the use of the newer electromagnetic microphone made for the talking picture laboratories. The new Siemens-Halske electromagnetic stethoscope, with a small aluminum plate for direct contact with the chest wall, has proved satisfactory

camera in a vertical plane. This is cut out to fit around the cylindric lens at 7 or 8 mm from the end and to extend to the bromide paper. A sheet of thin metal is attached to the outer face of the camera, also in the same vertical plane, and along the inner side of the glow tube, thus preventing the glow from spreading across to the galvanometer portion of the film. Although the cylindric lens concentrates the light to a fairly fine line, better definition is obtained by fitting a copper plate in the sound tract portion so that it presses against the paper. In this plate is cut a horizontal slit 0.2 mm or less in width and held in the center of the line of concentrated light by support from the camera case. Better optical systems of glass or quartz may be purchased from the sound recording-machine manufacturers. The foregoing is a description of an adaptation for a particular electrocardiographic machine. Each type of camera would need its own design to isolate the sound tract. In the amplifying tube type of electrocardiograph, where the amplifier is built in the same case as the camera, it is necessary to surround the tube and its lead-in wires with metallic shielding.

The apparatus is remarkably stable and easy to handle. There are no delicate strings to protect and adjust. The tube is simply and ruggedly made. It need not be altered in position after once placed. It has a long life, gradually losing photographic power only after several hundred hours of operation. The life of the tube may be prolonged by operating it at a low milliamperage.

The tube is caused to glow by passing more current through it than is later necessary to maintain it. The time required to start the electron stream in the cold tube can be greatly reduced by exposing it to light from a flash light. If a metal shielding is used around the argon tube, a small aperture on top will permit inspection of the evenness of the glow during the silent periods and the cyclic recurrence of the first and second heart sounds, as shown by the flaring and dimming of the glow. This will serve as a check on the correct working of the apparatus before records are taken. The sound tract can be further standardized for lack of distortion and for intensity by recording strips from a known normal heart, or by recording the tone of a tuning fork, or by passing a millivolt from the electrocardiograph's standardizing current through the amplifier. The sound tract can therefore be read not only for its time relations, but also for intensity and frequency or pitch.

The routine here has been to record the three most commonly auscultated points of the precordium, i.e., the second right interspace near the sternum, the third left interspace also close to the sternum and the area of the apex as determined by the point of maximum impulse. These are recorded simultaneously with the first, second and third leads, respectively.

All records have been checked by careful stethoscopic findings and descriptions of the sounds, and where records have been found defective, the cause has generally been due to improper application of the stethoscope to the precordium or to excessive or insufficient amplification.

#### THE RECORDS AND THEIR INTERPRETATION

The normal tones at the apex are shown in figure 2 as a series of fine, vertical light and dark bands on the gray tract at the upper border of the electrocardiogram. The first change from the even gray of the silent period, whether it is dark or white, is the initial vibration of the sound. To compare with the string shadow deflections, the dark band corresponds to the portion above the iso-electric line and the white to the portion below. Records taken by this method do not differ from

former records taken by methods which did not introduce distortion. They are comparable in duration, in frequency (as measured by the number of bands per unit of time), as to intensity (as measured by relative degrees of light and darkness of the bands) and as to the time relations between the sounds and the electrocardiograms.

Figure 3 shows the tracings of the sounds at the second right interspace, obtained from a patient with aortic stenosis and auricular fibrillation. The star shows a long, high-pitched, systolic murmur. The second heart sound is almost imperceptible, as is commonly the case in

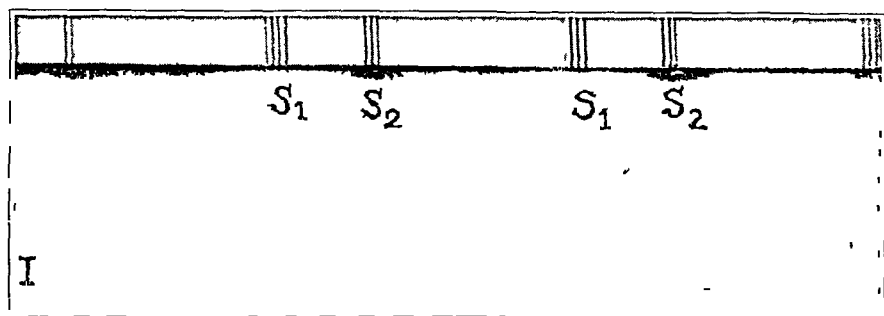


Fig 2—The upper tracing shows sound record (apex region) and below it the electrocardiogram (lead I) of a normal subject.  $S_1$  and  $S_2$  are the first and second heart sounds.

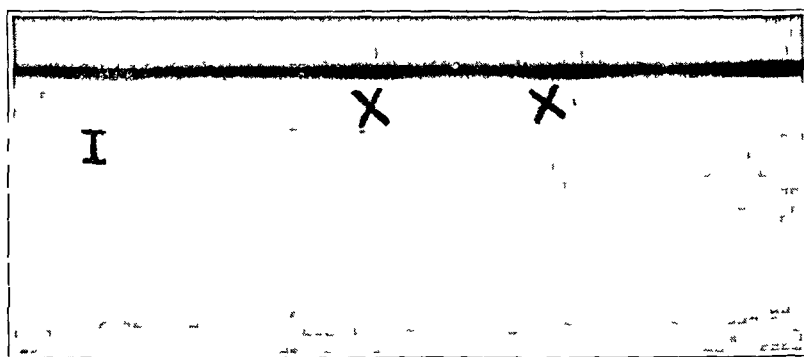


Fig 3—The upper sound record shows a prominent systolic murmur from the second right interspace.

aortic stenosis. Figure 4, taken at the third left interspace in the same case as figure 3, shows a premature ventricular beat producing an increased intensity or snapping quality of the first heart sound, which is well indicated in the sound tracing marked by the cross. The circles in the figure point to the presence of a short faint diastolic murmur of aortic insufficiency. The latter part of diastole or presystole was clear. It is necessary to have the patient hold his breath while taking records from the base of the heart to avoid the interference of respiratory sounds.

In figure 5 are shown the tracings of a patient with mitral stenosis and auricular fibrillation, before and after regularization by quinidine. The sound tracings were obtained at the region of the apex. The point marked X in the upper tracing shows a presystolic interval without a

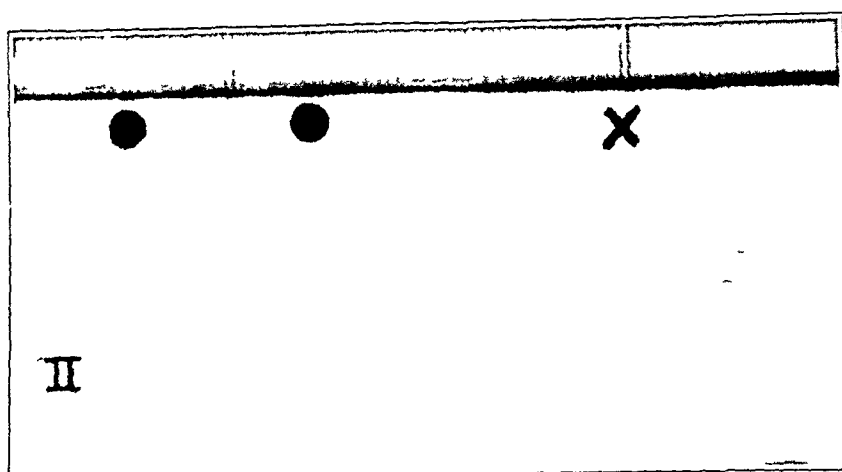


Fig. 4—The sound record from the third left interspace shows at the circles a short, faint diastolic murmur, and the X indicates an accentuation of the first heart sound from a premature beat. The patient had aortic stenosis and insufficiency.

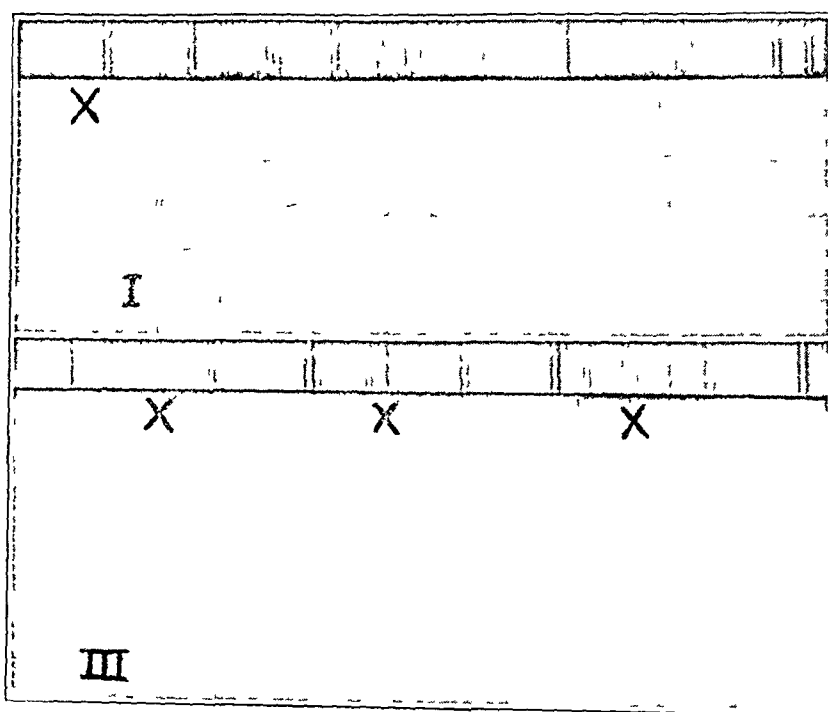


Fig. 5—Sound records from a case of mitral stenosis and auricular fibrillation. The upper record shows a clear interval in presystole marked X. The lower record, made with the heart regularized by quinidine, shows a constant presystolic murmur marked X.

murmur. This occurred only in the longer pauses. In the lower tracing when the heart rhythm was regular after the administration of quinidine the presystolic murmur was always present as shown at the times marked X.



The sound record shown in figure 6 was taken at the third inter-space of a patient with active rheumatic carditis. It shows a greatly accentuated second heart sound, marked  $S_2$ . A short, high-pitched murmur follows this sound, the clinical significance of which was difficult to determine. The P-R interval in this case was 0.25 second.

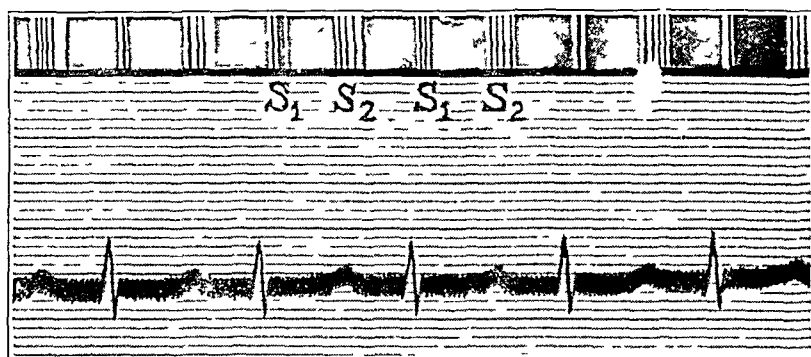


Fig. 6—Note the accentuation of the second heart sound followed by a short diastolic murmur.

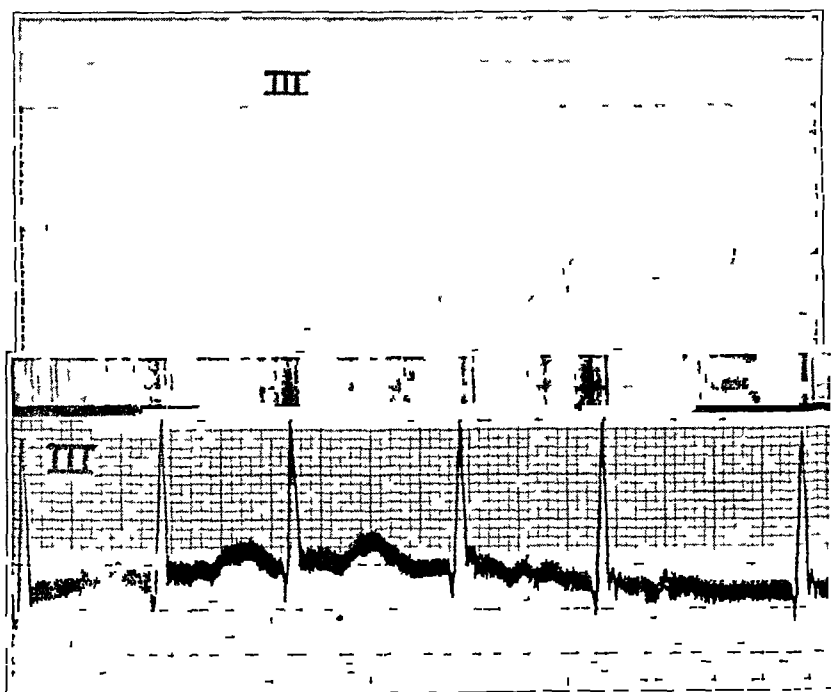


Fig. 7—The upper record shows the murmurs of mitral stenosis and auricular fibrillation before cardiolytic treatment and the lower record, after cardiolytic treatment. Note the increase in intensity of the diastolic murmur after the ribs were removed.

Figure 7 illustrates the apical sounds in a case of decompensated mitral stenosis with auricular fibrillation. The systolic and diastolic murmurs are loud and long, the systolic lasting up to the diastolic and the diastolic running through varying portions of diastole, the pre-systolic period being clear in the longer diastolic intervals.

The lower tracing was taken one month after cardiolysis, following a marked subjective and objective improvement took place. The cartilaginous and bony structures were gone, and these sounds were recorded through the thin, heaving precordium by allowing a Bowles type of chest-piece to rest by its own weight on the precordium, the heaving thrust of the heart being thus largely eliminated. Under such circumstances the resulting sounds must closely resemble the intrinsic vibrations of the wall of the heart as if the exposed heart were directly auscultated. Little change in the diastolic murmur was noted.

Experience with the patient represented by figure 8 proved rather instructive. The patient was a man, admitted to the hospital for paroxysmal dyspnea and congestive heart failure. His chest was emphysematous and filled with "noisy" râles, making auscultation difficult. At that time, a faint protodiastolic gallop was heard at the apex,

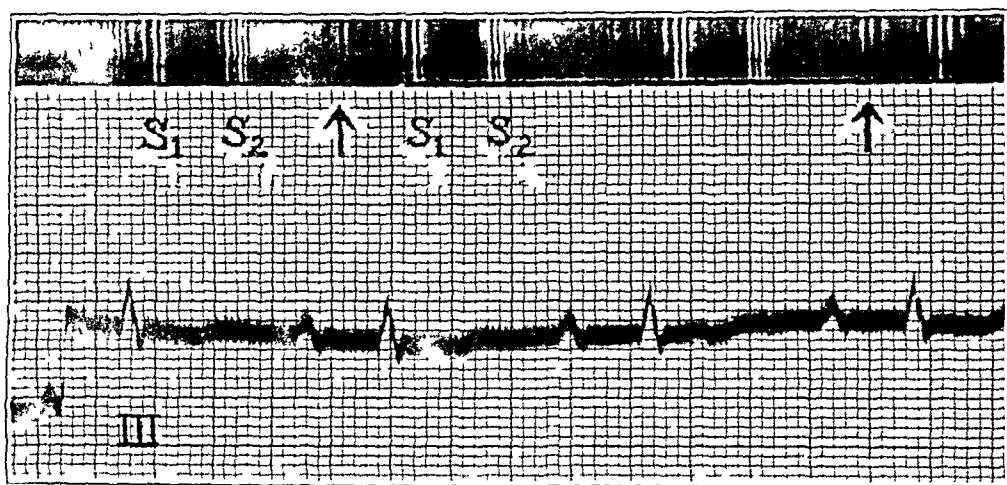


Fig 8—In the sound record the arrows point to a definite late diastolic murmur which was interpreted clinically as a gallop rhythm

but at the time of the sound record, therapy had slowed the heart and the gallop was termed late diastolic. A tentative diagnosis of myocardial deficiency without valvular disease was made. The patient had, however, the mitral facies, and the electrocardiogram showed right axis deviation and wide, notched P waves. In this case the sound records proved valuable, in that a definite murmur was detected in late diastole, which in time, was related to auricular systole<sup>3</sup>. This suggested the possibility of mitral stenosis, and on subsequent clinical examination when the chest was clearer and auscultation more satisfactory, this murmur was more distinct and sufficiently characteristic to warrant the diagnosis of mitral stenosis. In this instance, the sound tracings proved to be helpful at a time when, from clinical examination alone, a wrong interpretation might have been made.

<sup>3</sup> Wolferth C. C., and Margolies, A. Various Types of "Extra" Heart Sounds, *M. Clin. North America* **14** 897 (Jan) 1931

The foregoing method of recording sounds has also been used to photograph the qualities of the first heart sounds in the presence of complete heart block with and without auricular fibrillation. In the former, the first sound was found to vary in different cycles and in the latter, it was found to be constant. The ease with which it may be employed in any electrocardiograph laboratory permits its use to testify as to the presence and character of a murmur in disputed diagnosis and insurance examinations. It also offers a method of further investigating the whole subject of gallop rhythm and other auscultatory phenomena met with in general medicine, such as cranial bruits, fetal heart sounds and arteriovenous murmurs.

#### CONCLUSIONS

A new method for photographing heart sounds has been described, the argon glow tube being used. Once the necessary apparatus was set up, the method was found to be simple. It could detect the ordinary and obscure heart sounds.

Illustrations of some of its uses in clinical cases are described and suggestions for its further applications are offered.

# AZOTEMIA DUE TO LOW BLOOD PRESSURE

## ITS OCCURRENCE IN AN UNUSUAL CASE OF ACUTE RHEUMATIC FEVER

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The occurrence of azotemia in the absence of nephritis is recognized and has been discussed extensively in the literature. Little attention, however, has been paid to the possibility of nitrogen retention in the blood being due primarily to anuria resulting from hypotension. Both Roch<sup>1</sup> and Merklen<sup>2</sup> in their papers on the subject call attention to anuria or oliguria as a frequent extrarenal cause of azotemia, but they do not mention hypotension among the causes for this oliguria. Azotemia due to hypotension appears to be a rare occurrence, or else blood studies with this point in mind have not been made in cases of marked hypotension. It seems probable that the latter is the case.

Studies<sup>3</sup> on the physiology of the kidney have shown that in the experimental animal a minimum blood pressure of from 30 to 40 mm of mercury is necessary for the secretion of urine. This figure corresponds remarkably to the osmotic resistance of the blood proteins in man, calculated at 30 mm by Starling in 1899. For this reason, it has been assumed that the minimum blood pressure required for urinary secretion is in man also from 30 to 40 mm. Clinical evidence on this point is quite meager, but it seems reasonable to suppose that as the blood pressure approaches or reaches this minimum level, there will result oliguria or anuria, which if maintained for any length of time will cause nitrogen retention in the blood. Muller-Deham<sup>4</sup> in 1922 presented clinical evidence of diminished kidney function in even relatively mild cases of hypotension. He studied cases of Addison's disease, carcinoma of the stomach and duodenal ulcer in which the blood pressure ranged between 60 and 105 systolic, and found the kidney function definitely impaired, as judged by urinary volume and power of concentration. He does not include blood studies in his paper.

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From the Medical Clinic of the Peter Bent Brigham Hospital

1 Roch, M. L'azotémie sans lésions rénales, *Rev méd de la Suisse Rom* 50 497 (July) 1930

2 Merklen, P. *Medecine* 3 760 (July) 1922

3 Cushny, A. R. *The Secretion of the Urine*, New York, Longmans, Green & Company, 1917, p 107

4 Muller-Deham, A. *Klinische Beobachtungen über Nierenfunction und Blutdrücksenkung*, *Wien Arch f inn Med* 3:323, 1922

There are two clinical conditions in which one might expect to find nitrogen retention resulting from hypotension. These are shock, medical or surgical, and, perhaps, Addison's disease.

Duval and Grigaut<sup>5</sup> in 1918 studied chemical analyses of the blood in cases of traumatic shock of varying intensity and duration in which the blood pressures ranged from 50 to 80 systolic and from 30 to 50 diastolic. They found the blood urea nitrogen and nonprotein nitrogen elevated, but only moderately so, hardly exceeding twice the normal figures. This elevation was interpreted as being due to the liberation of, nitrogenous materials from the traumatized tissues. Aub and Wu<sup>6</sup> in 1920 found only slight elevation of blood urea in experimentally produced traumatic shock in cats, and control animals in which a corresponding lowering of blood pressure was produced by intrapericardial pressure showed no elevation of blood urea. Garofeanu and Lazar<sup>7</sup> in 1926 studied the blood urea of dogs in peptone shock, samples of blood being withdrawn from twenty to thirty minutes after the establishment of shock, and found a slight increase in a few cases, but a definite decrease in most cases. This decrease they considered as probably due to the loss of the plasma which carries the main part of the urea into the tissues. The failure to find a marked azotemia in these instances of traumatic shock may be due to the fact that the blood pressure did not fall sufficiently low or else had not remained low for a sufficient period before the blood analyses were made.

The occurrence of shock in certain medical conditions was demonstrated by Janeway<sup>8</sup> in 1907 and more recently by Atchley<sup>9</sup> in 1930. The latter pointed out the associated inhibition of renal function, and in the report of one of his cases he mentioned a rapid rise in the blood urea nitrogen following the establishment of anuria. Evans<sup>10</sup> recently reported the occurrence of azotemia in a patient who on the sixth day after an operation for appendical abscess went into a state of circulatory collapse, which persisted intermittently, with the blood pressure falling as low as 50 systolic, for approximately fourteen hours before death. Although the nonprotein nitrogen rose to 240 mg per hundred cubic

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5 Duval, P., and Grigaut, A. L'intoxication par les plaies de guerre, La retention azotée des blessés, *Compt rend Soc de biol* **81** 873, 1918.

6 Aub, J. C., and Wu, H. Studies in Experimental Traumatic Shock, *Am J Physiol* **54** 416 (Dec) 1920.

7 Garofeanu, M., and Lazar, N. Les variations de l'urée sanguine au cours du choc peptonique chez le chien, *Compt rend Soc de biol* **95** 427 (July) 1926.

8 Janeway, T. C. Some Common Misconceptions in the Pathological Physiology of the Circulation and Their Practical Significance, *New York M J* **85** 193, 1907.

9 Atchley, D. W. Medical Shock, *J A M A* **95** 385 (Aug 9) 1930.

10 Evans, T. S. Azotemia with Normal Kidneys Found Post Mortem, Possible Cause Low Blood Pressure After Operation, *Arch Int Med* **48** 1231 (Dec) 1931.

centimeters, postmortem examination revealed essentially normal kidneys, so it was thought most probable that the renal insufficiency had been due to hypotension.

It has been shown by several observers that experimental extirpation of the renal glands is followed by a marked rise in blood urea nitrogen without evidence of nephritis. Marshall and Davis,<sup>11</sup> in 1916, found no relation between this nitrogen retention and the blood pressure level, and concluded that hypotension was not an important factor in this azotemia, but that the adrenals must normally exert a favorable influence over the function of the kidneys. Nitrogen retention in cases of Addison's disease has been a frequent observation, and this occurrence in the absence of nephritis has given rise to considerable speculation and study. Sicard and Haguénau<sup>12</sup> in 1914 reported blood nonprotein nitrogen values of 245 and 200 mg per hundred cubic centimeters in two cases of Addison's disease in which the urine showed no evidence of nephritis and in one of which autopsy revealed no appreciable renal lesions. Rowntree,<sup>13</sup> in 1925, studied the renal function in twelve cases of Addison's disease and found the blood urea nitrogen elevated above 30 mg in ten cases, above 50 mg in four cases and between 90 and 100 mg in two cases. Although the phthalein excretion was normal in all but two cases, additional evidence of renal insufficiency was shown by a diminished urinary output. The urine in these cases was essentially normal, and postmortem examination in several showed no evidence of nephritis. The blood pressure in these cases averaged 90 systolic and 62 diastolic, the lowest readings being 60 systolic and 40 diastolic. Rowntree ventures the opinion that "since organic pathological evidence is usually lacking, diminished renal function is probably an accompaniment of the low blood pressure and the resulting circulatory disturbance." Mozer<sup>14</sup> in 1929 reported three cases of azotemia in Addison's disease with blood nonprotein nitrogen readings of 260, 80 and 79 mg per hundred cubic centimeters, all of which had negligible urinary findings and showed essentially normal kidneys at autopsy. Mozer feels that hypotension alone cannot account for the renal insufficiency in these cases, basing this contention on the fact that there was no appreciable oliguria in his three cases and on the fact that transient hypotension in acute infectious conditions is frequently not accompanied by evidence of renal insufficiency. He cites a case of chronic hypotension (from 65 systolic and

11 Marshall, E K, Jr, and Davis, D M. The Influence of the Adrenals on the Kidneys. *J Pharmacol & Exper Therap* 8 526 (Sept) 1916.

12 Sicard, J A, and Haguénau. Dosage de l'urée sanguine des addisoniens, *Bull et mem Soc méd d hôp de Paris* 37 902, 1914.

13 Rowntree, L G. Studies in Addison's Disease, *J A M A* 84 327 (Jan 31) 1925.

14 Mozer, J J. De l'influence de la surrénale sur le fonctionnement du rein; syndrome azotémique addisonien, *Presse méd* 37 156 (Feb 2) 1929.

30 diastolic to 70 systolic and 40 diastolic) in a girl with an endocrine disturbance who showed a normal blood urea nitrogen and a normal phthalein excretion. He concludes, in accord with Marshall and Davis,<sup>11</sup> that there must be a suprarenal influence on renal function without which the kidneys fail to perform their work properly.

The following case is of interest in that it presents the same phenomenon noted by Evans,<sup>10</sup> but with recovery, and because it represents what seems to be a manifestation of acute rheumatic fever of unusual severity.

#### REPORT OF A CASE

*History*—On July 30, 1931, an Italian-born laborer, aged 23, was brought to the medical clinic of the Peter Bent Brigham Hospital in a stuporous condition with a history of vomiting for five days accompanied by fever and pains in the joints. He had previously been in good health, with no history of disease or exposure to industrial poisons, and had been taken ill rather suddenly while at work with a road construction gang.

*Examination*—On admission, he presented the picture of extreme circulatory collapse. He was apathetic, though somewhat restless, and could be partially roused only with difficulty. The extremities were cold and cyanotic, the radial pulse could not be felt, and no blood pressure reading could be obtained. The heart sounds were faint, quite rapid (140) and tic-tac in quality, and there was a pericardial friction rub in the pulmonic region. There were no demonstrable cardiac enlargement and no peripheral edema or congestion of the lungs. The temperature was 100 F by rectum and the respiratory rate, 35. The patient was markedly dehydrated, as evidenced by a red blood cell count of 7,000,000 with a hemoglobin of 125 per cent (Sahli), and there was a leukocytosis of 24,000 with 83 per cent polymorphonuclears. Although he had last voided about five or six hours before admission, catheterization yielded only 5 cc of clear urine, which on analysis showed the slightest possible trace of albumin but no cells or casts.

An electrocardiogram showed normal curves, a lumbar puncture gave normal findings, the Wassermann and Hinton tests of the blood were negative, and two blood cultures were negative.

*Course*—The patient vomited only once after admission, but in spite of the fact that he retained considerable amounts of fluid by mouth, he was given during the first thirty-six hours tap water by rectal drip, 3,000 cc of Ringer's solution by clysis and 100 cc of 50 per cent dextrose intravenously. At the end of this period his condition remained essentially unaltered, the blood pressure was still not recordable, and there was almost complete anuria demonstrated by a second catheterization yielding but 4 cc of urine, which like the first showed a slight amount of albumin but no red cells or casts. A blood urea nitrogen determination at this time showed 75 mg per hundred cubic centimeters.

On the third day, following a clysis of 1,500 cc of Ringer's solution accompanied by 50 cc of 50 per cent dextrose intravenously, there was striking clinical improvement, the cyanosis disappeared, a weak pulse could be felt at the wrist, and the blood pressure was obtained for the first time, with a reading of 100 systolic and 80 diastolic. Five hundred cubic centimeters of urine was passed, which showed in addition to a slight trace of albumin a few red blood cells (from 1 to 2 per high power field), but no casts.

In spite of progressive clinical improvement and a good urinary output, a second blood urea nitrogen determination on the fifth day showed a rise to 119

mg per hundred cubic centimeters. It then gradually fell to normal, reaching 65.8 mg on the eighth day and 12.6 mg on the twelfth day. The urine gradually cleared, becoming entirely normal on the fifteenth day and remaining so for the remainder of the period of observation. The phenolsulphonphthalein excretion was slightly depressed (25 per cent) on the fifth day, but subsequent determinations were normal (from 40 to 65 per cent). Further blood studies on the eighth day showed a carbon dioxide-combining power of 60.7 per cent by volume, and the blood sodium chloride to be 350 mg per hundred cubic centimeters.

The temperature dropped to normal on the third day, but on the fifth day again rose, reaching 102.5 F on the sixth day, when there appeared a generalized morbilliform rash, bright red, macular, nonitching and evenly distributed over the whole body, including the palms and the soles. The eruption became largely confluent and faded out entirely in the course of a week. The temperature again subsided, but continued to be slightly elevated up to the time of the patient's discharge on the thirty-ninth day after admission. The leukocytosis continued, reaching 33,000 on the eighth day and gradually dropping to 18,000 on discharge. The pericardial rub disappeared several days after admission, and on discharge the heart sounds were normal, except for a slight, persistent tachycardia.

The patient was seen four months later, and although apparently in the best of health, still showed a tachycardia of from 90 to 110 and a leukocytosis of from 16,000 to 18,000.

#### COMMENT

The fever and leukocytosis, with the absence of a history of poisoning indicated some sort of an infection, while the history of transient joint symptoms, the pericardial rub, the morbilliform rash and the subsequent chronicity of the infection, all pointed to acute rheumatic fever.

It seems justifiable to assume that azotemia occurred in this patient in the absence of nephritis, the scant urinary findings being due to the general toxic reaction with simple cloudy swelling of the tubular epithelium. However, the nitrogen retention was probably not due to the marked hypotension alone. Blum<sup>15</sup> has called attention to the rôle of a lowered sodium chloride level in the blood in the production of the azotemia seen in cases of persistent vomiting or diarrhea. He explains this nitrogen retention as being a defense reaction to maintain the proper molecular concentration of the blood. With the history of persistent vomiting prior to admission and the lowered blood sodium chloride level a week after admission, this factor doubtless played a part in the production of the azotemia in this case. However, the marked rise in the blood urea in spite of the administration of large quantities of Ringer's solution by clysis and in the absence of further vomiting indicates that the anuria of hypotension was probably the main factor in this nitrogen retention.

<sup>15</sup> Blum L., Grabar, P., and van Coulaert. L'azotémie par manque du sel, son mécanisme, *Ann de med* 25 34 (Jan) 1929.



# CHRONIC ARTHRITIS

A CLINICAL ANALYSIS OF THREE HUNDRED AND  
FIFTY CASES

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MINNEAPOLIS

In considering any study of arthritis it seems advisable to define the term as used, as it obviously means different things to different persons. My conception of arthritis is that it is a disease probably of infectious origin. Etiologic evidence is accumulating which points strongly toward the streptococcus as being the causative agent in the majority of cases of arthritis, including acute cases that are termed rheumatic fever as well as chronic arthritis. The literature covering the etiologic evidence for streptococcic infection has been reviewed by Clawson<sup>1</sup> for rheumatic fever and by Clawson and me<sup>2</sup> for chronic arthritis. Jordan<sup>3</sup> and Poynton and Schlesinger<sup>4</sup> have also reviewed the literature of the microbic origin of these conditions. There is no doubt but that other organisms such as the gonococcus and *Bacillus tuberculosis* may produce a type of arthritis that occasionally simulates streptococcic arthritis. It is also known that other organisms, such as the pneumococcus, staphylococcus, dysentery bacillus, typhoid bacillus and probably the spirochete, are causative in occasional cases. The evidence would signify, however, that a high percentage of all cases of acute and chronic arthritis are due to streptococcic infection. The exact nature of this infection has not been entirely clear, some investigators contending that the organic changes in the joints might be due to an allergic reaction alone and not to the presence of actual bacterial invasion. From recent investigations it seems more likely that streptococcic arthritis is dependent on the actual presence of organisms, and that the allergic or hypersensitive factor is of secondary importance. It is apparent that the clinical and pathologic manifestations of strepto-

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1 Clawson, B J. Bacteriology of Acute Rheumatic Fever with an Experimental Basis in Animals for Vaccine Therapy, *Minnesota Med* **14** 1, 1931

2 Clawson, B J, and Wetherby, Macnider. An Experimental Basis for Intravenous Vaccine Therapy in Chronic Arthritis with a Summary of Results Obtained in Patients, *Ann Int Med* **5** 1447, 1932

3 Jordan, E P. The Microbic Etiology of Rheumatic Fever and Arthritis, *Arch Path* **10** 79 (July) 1930

4 Poynton, F J, and Schlesinger, B. Recent Advances in the Study of Rheumatism, Philadelphia, P. Blakiston's Son & Co., 1931

coccic arthritis may present many variations dependent on secondary factors, such as age, climate, trauma, exposure, individual susceptibility and resistance, the virulence of the organism and the extent of the inciting infection Rolleston<sup>5</sup> has expressed the following opinion

On the whole, it might be reasonable to suggest that varying degrees of diminished constitutional resistance of the fibrous tissues or sensitization to infection on the one hand, and on the other hand, the action of different kinds of streptococci might explain the different clinical manifestations seen among the diseases grouped for convenience under the head of rheumatism

The terminology in use for arthritis has been a subject of confusion, owing to the absence of an accepted etiologic classification The classifications generally used are that of Garrod<sup>6</sup> adopted by the British Ministry of Health and those of Goldthwait<sup>7</sup> and Nichols and Richardson<sup>8</sup>

#### *Classifications of Arthritis*

British	Goldthwait	Nichols and Richardson
I Rheumatic Fever		
II Rheumatoid	} Infectious { } Atrophic {	Proliferative
III Osteo-arthritis	Hypertrophic	Degenerative

The preceding classifications are not in true corollary groups because of the different criteria for selection Nichols and Richardson's study was made on a pathologic basis, without regard to the etiologic nature They recognized similar pathologic changes produced by different agents Goldthwait has included gonorrheal arthritis under the infectious group The British classification has dealt with only so-called nonspecific arthritis Using the terminology of the British classification, I concur with Cecil<sup>9</sup> in the opinion that the cases of clinical rheumatoid arthritis are due to streptococci The term osteo-arthritis has apparently been used to cover conditions with various causes Unfortunately, some clinicians use this term to include senescent changes, pure traumatic damage in the joints and changes produced by articular hemorrhage from purpura or hemophilia I believe that most of the cases with pains of the joints, clinically termed osteo-arthritis are only variations

<sup>5</sup> Rolleston, H D Rheumatic Diseases, Lancet 2 1016, 1928

<sup>6</sup> Garrod, A E, in Albutt, T C, and Rolleston, H D A System of Medicine, New York, The Macmillan Company, 1910, vol 3, p 3

<sup>7</sup> Goldthwait, J E, Painter, C F, and Osgood, R B Diseases of the Bones and Joints, Boston, D C Heath & Company, 1909

<sup>8</sup> Nichols, E H, and Richardson, F L Arthritis Deformans, J M Research 26 149, 1909

<sup>9</sup> Cecil, R L, Nicholls, E E, and Stainsby, W J The Etiology of Rheumatoid Arthritis, Am J M Sc 181 12, 1931

of streptococcic arthritis, largely in older persons in whom chondro-osseous changes predominate, and that there is not a sharp line of distinction between such cases and those termed rheumatoid arthritis. Clawson<sup>10</sup> has isolated streptococci from the blood and subcutaneous nodules of older persons with predominant hypertrophic changes that might be termed osteo-arthritis according to the popular clinical and roentgenologic criteria of differentiation. McCrae<sup>11</sup> and Timbrell Fisher,<sup>12</sup> on the basis of clinical and pathologic studies, have expressed the opinion that a high percentage of persons with chronic arthritis have involvement of the mixed type. Fisher, in 1928, prior to much of the recent etiologic investigation, advised the use of the general term chronic arthritis. McCrae has stated his inability to place patients in two distinct clinical groups. With the aforementioned considerations in mind, a clinical analysis has been made of 350 consecutive cases of arthritis seen in the outpatient department of the University of Minnesota Hospital during the past year. The patients were admitted chiefly for intravenous streptococcic vaccination, which has been discussed in previous papers<sup>13</sup>. No selection of patients was made other than that those chosen had had nontraumatic pain in the joints for at least two months, and no one was included who gave clinical evidence of a specific type of infection such as gonorrhea or tuberculosis. Relatively few cases of such types were met with in this series. The material represents a clinical cross-section of that large group of conditions sometimes termed nonspecific arthritis. Muscular pain was not infrequent in this group, and in the patients with more serious involvement, the articular condition was apparently only a prominent local manifestation of a constitutional disease. As a routine, a record was made in every instance to obtain information concerning sex, present age, age at onset, duration, history of probable streptococcic infections, trauma as an inciting factor, previous therapy, joints involved, the first joint or joints involved, the joints most severely involved, the degree and type of articular involvement, roentgen studies, observations on the heart and possible associated conditions. In the last 300 cases, a thorough routine search was made for subcutaneous nodules.

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10 (a) Wetherby, Macnider, and Clawson, B. J. Chronic Arthritis, with Special Reference to Vaccine Therapy, *Arch Int Med* **49** 303 (Feb.) 1932. (b) Clawson, B. J., and Wetherby, Macnider. Subcutaneous Nodules in Chronic Arthritis, *Am J Path* **8** 283, 1932.

11 McCrae, T., in Osler, W., and McCrae, T. *Modern Medicine*, Philadelphia, Lea & Febiger, 1915, vol. 5, p. 895.

12 Fisher, A. G. Timbrell. *Chronic (Non-Tuberculous) Arthritis*, New York, The Macmillan Company, 1929.

13 Clawson and Wetherby.<sup>2</sup> Wetherby and Clawson<sup>10a</sup>, Intravenous Streptococcic Vaccine Therapy in Chronic Arthritis, *J A M A* **98** 1974 (June 4) 1932.

## CLINICAL FINDINGS

*Sex Incidence*—In the series of 350 persons, 240 were women (68.57 per cent) and 110 were men (31.43 per cent). It is of interest that during this period the sex ratio of patients admitted to the outpatient department was approximately 57 per cent women and 43 per cent men. Most of the patients in our series came definitely for intravenous streptococcic vaccine therapy, so that the sex difference of the total admissions to the dispensary is hardly applicable in explaining the marked preponderance of females among arthritic patients. The possibility was considered that women might seek relief for less severe symptoms than men. On careful analysis this does not seem to be the case, as the duration of symptoms was determined and found to be about the same for the two sexes. A similar preponderance of females has been found in large series of cases by the Cambridge Committee,<sup>14</sup> Garrod,<sup>15</sup> Llewellyn Jones,<sup>16</sup> Cecil and Archer<sup>17</sup> and Pemberton and Pierce.<sup>18</sup> McCrae,<sup>11</sup> however, found no marked difference in incidence in the two sexes.

*Age of Patients*—In considering the age of arthritic patients, it has seemed advisable to determine both the age at onset and the age at the time of admission to the hospital. This has been done for men and women separately, no striking differences between the two sexes has been found, the peak for both appearing in the fifth decade when the age of onset is considered and about evenly divided between the fifth and sixth decades when the present age is considered. Pemberton and Pierce<sup>18</sup> and Garrod<sup>15</sup> also found the peak of onset to occur about as in this series. In McCrae's<sup>11</sup> series the peak of onset was in the third and fourth decades.

*Duration of Arthritic Symptoms*—The duration of articular symptoms in men and women was determined separately and in a total group. There was found to be no marked difference in the duration of arthritis in the two sexes at the time of admission to the outpatient department. It is of interest that 55.2 per cent of the total group had had arthritic symptoms more than five years before admission to the hospital, and that only 12.3 per cent had had a history of less than one year's duration.

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<sup>14</sup> Cambridge Committee Report, cited by McCrae (footnote 12, p. 899)

<sup>15</sup> Garrod, A. E. *A Treatise on Rheumatism and Rheumatoid Arthritis*, London, Charles Griffen Company, London, 1890.

<sup>16</sup> Jones, R. Llewellyn. *Arthritis Deformans*, New York, William Wood and Company, 1909.

<sup>17</sup> Cecil, R. L., and Archer, B. H. *The Classification and Treatment of Chronic Arthritis*, J. A. M. A. **87**: 741 (Sept. 4) 1926.

<sup>18</sup> Pemberton, Ralph, and Pierce, E. G. *A Clinical Study of Chronic Arthritis Based on Eleven Hundred Cases*, Am. J. M. Sc. **173**: 31, 1927.

*Incidence of Distribution of Involvement in Various Joints*—There are many popular clinical impressions in regard to the details of involvement of the joints in chronic arthritis Garrod<sup>15</sup> and Pemberton and Pierce<sup>18</sup> have previously tabulated the incidence of involvement of the individual joints

In this series a detailed routine history of pain in the joints was taken in each case. A joint was considered to be involved if it had been the location of pain at some time during the course of the disease. The incidence of monarticular or polyarticular involvement was determined, and it was found that only 5 patients of a total of 350 had involvement of a single joint. In a small percentage of cases the symptoms were predominant in a single joint, but the condition could not be strictly interpreted as one of monarticular involvement.

The average number of joints involved in a patient was determined for men and women separately, the spine, fingers, toes, hands or feet of one side being counted as only one joint. There was no striking difference in the total number of joints involved for the two sexes, in women the average was 10.9 joints for each patient, and in men, 10 joints.

In the great majority of patients the involvement of the joints was bilaterally symmetrical in distribution, but not necessarily of equal degree on both sides. The relative distribution of the involvement in men and women was determined separately and in a composite group. It was noted that in both sexes the knees were more commonly affected than any other joints, there being involvement of the knee in 290, or 82.8 per cent, of the entire group of 350 persons. The fingers were next most commonly involved in the total group, being affected in 61.1 per cent of the cases.

There was a difference between the two sexes in the incidence of involvement of joints. The percentage of involvement of individual joints in the two sexes is given in table 1.

In the women there was a significant predominance over the men of involvement of the fingers, hands and toes, while in the men there was relatively more frequent involvement of the feet, hips and spine. The cervical part of the spine was more frequently mentioned as being involved than any other portion.

The incidence of joints initially involved was determined for men and women separately. The patients sometimes mentioned more than one joint as being involved at the onset. If only two joints were mentioned, they were recorded separately. If three or more joints were mentioned, the initial involvement was expressed as multiple. The knees were the first joints involved in 27.5 per cent of the men and 19.1 per cent of the women. Next the fingers were most often the first joints affected, and in the women they were almost as frequently

the first involved as were the knees. The fingers were first involved in 24.2 per cent of the women and in 7.3 per cent of the men. In the men, however, the spine, ankles and shoulders were more commonly initially affected than were the fingers.

A tabulation was also made of the joints most severely involved at the time of the examination. The knees again were most often mentioned by 33.3 per cent of the women and 22.7 per cent of the men. The spine was nearly as often the most severely affected in men. It is of significance that the spinal involvement was the most marked in 20 per cent of the men and in only 5.8 per cent of the women. The hips were also much more frequently the joints seriously involved in men (17.3 per cent) than in women (7.1 per cent). However, the fingers were frequently the most severely affected in women (16.6 per cent),

TABLE 1—*Percentage of Involvement of Individual Joints in Two Sexes*

	Men (110) per Cent	Women (240) per Cent
Fingers	44.5	68.7
Hands	38.2	41.2
Wrists	46.3	51.7
Elbows	40.0	43.3
Shoulders	56.4	57.5
Toes	27.3	37.1
Feet	34.5	27.9
Ankles	56.4	59.6
Knees	77.3	85.4
Hips	50.0	42.1
Spine	69.1	51.7
Sacro iliacs	29.1	25.8
Jaws	9.1	12.5
Sternoclavicular	3.6	2.0

while in only one man (0.9 per cent) was the involvement of the fingers the most severe.

A comparison was made of unilateral articular involvement in the right and left extremities. There was apparently no significant differences in the right and left lower extremities in any of the groups tabulated. In the upper extremities there was no significant difference between the right and left in the number of joints involved and in the incidence of the joints most severely affected. However, there was an initial involvement of the right upper extremity in 59 cases as compared with 16 cases in which the left upper extremity was first involved. A possible explanation might be that the right upper extremity is usually subjected to greater trauma, and that this may be an inciting factor either in the onset or in the location of the clinical signs of arthritis.

Many general opinions are given as to the frequency of involvement of certain joints in persons in whom arthritis occurs at different ages. A study was made to show the incidence of involvement of joints in men and women separately, the age of onset by decades being considered. In general, it was found that there were few striking differences in the

percentage of involvement of individual joints in the various age groups. The striking sex differences in involvement of the joints are present in nearly all of the age groups. An exception is the observation that the incidence of spinal involvement in women in whom the onset of arthritis occurred between the ages of 20 and 39 years was as great as that in men of that period, while in the age groups 10 to 19 and 40 to 69 there was a marked predominance of involvement of the spine in men. The knees were found to be involved in a higher percentage than other joints in both men and women in all age groups. The fingers were involved in a high percentage of women in all age groups.

There is much discussion of the tendency toward unilateral involvement of the joints among persons acquiring arthritis after 50 years of age. The incidence of unilateral involvement in men and women of various age groups is shown in table 2. Unilateral involvement was found to be more common in women acquiring arthritis in the later decades of life, but no such difference was found in men.

TABLE 2—*Unilateral Involvement of Joints Tabulated According to Age Groups*

Age Group	Men, per Cent	Women, per Cent
10-19	14	14
20-29	17	10
30-39	19	12
40-49	12	13
50-59	12	18
60-69		23

The number of joints involved in each arthritic patient was compared in persons acquiring arthritis in different decades of life. In estimating this factor, the fingers or toes of one side and the joints of a hand or a foot were counted as one joint, as was involvement of the spine. Allowance was made for unilateral and bilateral involvement. There were found to be no striking differences in men in the number of joints affected in each decade, although in women acquiring arthritis in the third and fourth decades there seemed to be a significantly greater number of joints involved than in women of other age groups.

*History of "Clinical Rheumatic Fever"*—In considering the incidence of rheumatic fever, one is confronted with a difficult problem and much controversy. In general, rheumatic fever is considered as acute involvement in and about the joints, usually polyarticular, which is transitory with associated fever and which subsides within a few weeks or months without the occurrence of permanent articular changes. There is a high incidence of involvement of the endocardium, myocardium and pericardium. Subcutaneous nodules are described in a significant percentage of cases. Rheumatic fever is fairly easily recognized as an entity in children, but it is increasingly difficult to dis-

tinguish it from acute and subacute involvement of the joints with residual changes occurring in adolescence and early adult life. Many such cases in young adults may be diagnosed as rheumatic fever at an early stage of the disease and later as "rheumatoid" (atrophic, proliferative, infectious) arthritis. In young adults in our group such experiences were common. Clinically, I am unable to place a sharp dividing line between cases termed rheumatic fever and those with an apparently similar onset that progress to chronic articular involvement. There are several cases in our group (to be described later) in which there was an acute transitory polyarticular involvement, fever, and a pathologic condition of the heart, with subsequent chronic damage of the joints starting at the time of the acute onset, there are a number of such cases without organic heart disease.

In 45 (12.9 per cent) of my series of 350 cases of chronic arthritis, there was a history of acute polyarticular involvement of the joints with fever and with subsidence of the symptoms in most of the joints within a few weeks or months. A number of these patients had two or more such attacks. In 13 cases there was no definite correlation of the acute attacks and the chronic involvement which appeared a number of years later. In 32 instances the acute attack preceded chronic involvement of the joints. In these instances, there was definite involvement of the heart in 6 cases and questionable involvement in another. All patients with questionable disease of the heart were studied carefully, orthodiagrams or roentgenograms taken at a distance of 6 feet from the patient and electrocardiographic study being employed. Three patients had definite disease of the mitral valves with presystolic murmurs and a contour of the heart characteristic of this condition. One patient, 73 years of age, who had acute involvement of the joints at 58, had a definite aortic insufficiency and a questionable involvement of the mitral valve as well. The Wassermann tests were negative, and there was no history or findings suggesting syphilis. Two persons had definite pericarditis, and one of them showed effusion. Roentgen examination of all of the patients described showed definite articular changes of arthritis. The patient with questionable involvement of the heart was a girl of 17, who had had an intermittent fever for three years which was acute in onset and accompanied by multiple articular pains. She had an average pulse rate of 120 a minute and a systolic murmur, and she was dyspneic on moderate exertion. The orthodiagram, however, was normal in size, and thick barium paste did not demonstrate left auricular enlargement. The incidence of rheumatic involvement of the heart in the 32 patients with chronic arthritis which was acute in onset was 18.7 per cent. There were no other cases of definite rheumatic involvement of the heart in the entire group of arthritic patients whose condition was of more insidious onset, except the case of a patient with mitral



stenosis from the group of those who had had acute involvement in the past without correlation with the subsequent chronic involvement. Therefore, the incidence of rheumatic involvement of the heart in the entire group is 7 cases in 350, or 2 per cent. McCrae<sup>11</sup> reported finding valvular heart disease in 40 of 500 cases of chronic arthritis, however, in some of these patients the disease was reported as being of non-rheumatic origin. There were a number of cases of cardiovascular heart disease in this series which were not included in the analysis.

The incidence of heart disease, while very small in the total group, is of some significance in the group of patients with chronic arthritis of acute onset. The ages of onset in this group and the types of condition are respectively as follows: 8, 9, 12, 13, mitral stenosis, 14, a questionable condition, 14, mitral stenosis, 17, 17, 17, 17, pericardial effusion, 18, 18, 19, 19, 20, 21, mitral stenosis, 22, 23, 24, 27, pericarditis, 31, 32, 35, 40, 42, 44, 45, 45, 50, 54, 58, aortic insufficiency and questionable mitral involvement.

The incidence of cardiac involvement in rheumatic fever is the strongest argument for the separation of rheumatic fever and more chronic types of arthritis as disease entities. It seems not unlikely, however, that this may not be a definite point of division, and that the age of the person is an important factor in determining the response of the tissues to similar organisms. There are probably many underlying factors determining the response of tissues to infection that are not well understood. In the case of involvement of the heart valves there is some anatomic basis for the infrequent involvement in older persons. Most investigators are of the opinion that the infection in the heart valves is usually produced by the lodgment of bacteria in the terminal arteries. Gross<sup>19</sup> has presented evidence that the musculature and the blood vessels of the heart valves undergo regressive changes in most persons during childhood, and that such vessels are usually absent in adults. He believes that this may be an important factor in the low incidence of the onset of involvement of the heart valves in older persons. This variation in tissue response seems to be true in nephritis as well as in arthritis, as chronic nephritis persists after acute involvement in about 50 per cent of adults and in only a small percentage of children. In general, in other infections, such as tuberculosis, there are definite differences in the response of the tissues of children and of older persons. The streptococci isolated from the blood, joints and subcutaneous nodules from patients with clinical rheumatic fever and the more chronic types of arthritis are apparently biologically related, in most instances, they exhibit cross-agglutinating reactions and cross-

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19 Gross, L. *The Blood Supply to the Heart in Its Anatomical and Clinical Aspects*, New York, Paul B. Hoeber, Inc., 1921.

protection in experimental animals. There is also evidence that these streptococci are not unrelated to streptococci causing other manifestations of disease.

The histologic appearance of tissue taken from the subcutaneous nodules of rheumatic and of chronically arthritic patients is similar in structure and not unlike that seen in the valves of the heart affected by acute rheumatism, according to Clawson<sup>10b</sup>. This phase will be discussed in more detail later, but it is mentioned here as a fact which strengthens the probability of a common etiologic basis for rheumatic fever and chronic forms of arthritis.

#### OTHER FACTORS ASSOCIATED WITH ARTHRITIS

*Association of Probable Streptococcic Infection with Arthritis*—Some of the infectious manifestations other than chronic arthritis which may be considered as of probable streptococcic origin are rheumatic fever, chorea, erythema nodosum, myositis, scarlet fever and erysipelas. These conditions do not always occur as entities, and there is some clinical overlapping. Tonsillitis, infections of the roots of the teeth and puerperal sepsis are believed to be due to streptococci. Glomerulonephritis is also considered by many as of streptococcic origin. There was a history of scarlet fever in 57 of 350 cases of arthritis (16.3 per cent). In 2 instances the scarlet fever was a definite forerunner of chronic arthritis indistinguishable clinically from other cases of arthritis. In one of these patients the initial involvement was acute, and now after three years the patient has a definite lesion of the mitral valve, mitral stenosis.

Chorea had been present in only 3 instances in the total series, less than 1 per cent. There was no pathologic condition of the heart in these 3 cases or any definite correlation with the chronic involvement of the joints which appeared later.

According to the histories obtained, dental infection was present in many patients, but it seemed a probable precursor of the arthritis in 17 cases. Such an infection may have been an inciting factor in many more instances, but it was not known to be present to a marked degree in the other cases. The selection of certain cases as being of etiologic significance is of course arbitrary, and after reviewing them, some physicians might believe that the infection was of significance in a much greater number.

Acute sinusitis immediately preceded the involvement of the joints in 13 persons. An acute respiratory infection immediately preceded the arthritis in 11 persons. Such infections were probably present more often and forgotten after a number of years, as most of the histories in which such infections were mentioned were those of patients with a recent onset of articular symptoms.

A history of tonsillitis at some time was present in a large number of patients, but probably in no higher percentage than among non-arthritic persons. In 7 instances, however, the tonsillitis immediately preceded the arthritis, in 3 of them, a peritonsillar abscess was present, and in 1 there was also an associated acute sinusitis.

There was a history of arthritis developing during and persisting following puerperal sepsis in 7 cases. The involvement of the joints was extensive and severe in nearly all of these patients. Arthritis developed immediately post partum in 7 women in whom there was no definite clinical sign of sepsis, in 1 of them thrombophlebitis was present.

There was involvement following other infections, such as peritonitis, erysipelas, erythema nodosum, cervical adenitis and thrombophlebitis. There was a history of some definite infection preceding the arthritic involvement in 70 instances. If the 32 cases are added in which the onset resembled that of acute rheumatic fever, a definite infection preceded the process in the joints in 102 patients or in 29.1 per cent of the total number. In some of these the acute onset was probably preceded by acute infections of the upper part of the respiratory tract, although such a history was given only occasionally.

One point in particular seems worthy of emphasis, namely, that acute infections which may be inciting causes of arthritis may clear up completely in a relatively short period, leaving the patient with infection of the joints which may persist for many years. In a number of cases, the involvement of the joints seemed to be only one evidence of a more general infectious process. Pleuritis, muscular pains, subcutaneous nodules and anemia were not infrequently found when these patients were observed for some time. In the majority of cases, the arthritis was insidious in onset and without a known definite inciting infection. It is true that on thorough search some infection might be found in the teeth, tonsils, sinuses, prostate gland, cervix, gallbladder and intestinal tract, but such infections can likewise be found in many nonarthritic persons. Investigators who have studied the streptococci from the tonsils of arthritic and nonarthritic patients have found no significant differences either in the cultural characteristics or in the incidence of occurrence.

Secondary factors other than a definite infection seem of importance in initiating the clinical symptoms of arthritis. This probably means that these factors allow that opportunist, the streptococcus, to invade the tissues of the joints. Exposure, fatigue and trauma have been given in the history in a number of cases as factors both in inciting and in aggravating the involvement of the joints. Dysfunction of the thyroid gland when present may have some effect on an arthritic process. Neither hyperthyroidism nor hypothyroidism was present in a significant

number of patients in this series. The influence of the menopause has seemed rather vague in our experience, it is true that there is a high incidence of onset of arthritis in women at that period, although it is not relatively higher than in men of the same age. No special type of clinical involvement was recognized in patients acquiring arthritis at that time. Predisposing constitutional factors difficult to evaluate accurately, such as arthritic heredity, asthenic stature, vasomotor constriction and sluggishness of the large bowel, are probably also worthy of consideration. Pemberton<sup>20</sup> is of the opinion that a diet high in carbohydrates may aggravate an arthritic condition.

*Trauma as an Inciting Factor*—Trauma has preceded many cases of arthritis. In some instances it has seemed to be a factor in establishing the clinical manifestations of disease of the joints. A history of trauma as a probable inciting cause of arthritis was present in 12 persons. From each there was a history of definite injury, usually to a single joint, which persisted and within a short period of time was followed by multiple articular pains. The probable basis for the arthritis was that the traumatized tissue was more easily invaded by a subsequent infection. The possible rôle of trauma in inciting a clinical arthritic process is further emphasized by the fact that initial involvement of the joints was found to be about the same in the right and in the left lower extremities, while the joints of the right upper extremity were initially involved four times as frequently as those of the left upper extremity. Assuming most persons to be right-handed, trauma should be more frequent and severe in the upper right extremity.

There were many reports of aggravation of arthritic symptoms due to trauma, and in certain cases an occupational traumatic influence was noted.

*Subcutaneous Nodules*—Subcutaneous nodules have been reported frequently in the past in clinical rheumatic fever and less frequently in chronic arthritis.

Hillier<sup>21</sup> (1868) was one of the first to describe these lesions. Meynet<sup>22</sup> (1875) first pointed out that they bore a direct relation to acute rheumatic fever. Coates and Coombs<sup>23</sup> considered subcutaneous nodules the specific manifestation of rheumatic fever.

<sup>20</sup> Pemberton, Ralph. *Arthritis and Rheumatoid Conditions. Their Nature and Treatment*, Philadelphia, Lea & Febiger, 1929.

<sup>21</sup> Hillier. *Diseases of Children*, London, J. Walton, 1868, cited by Jacki, E. *Frankfurt Ztschr f Path* **22** 82, 1919.

<sup>22</sup> Meynet, P. *Rheumatisme articulaire subaigu avec production de tumeurs multiples*, Lyon méd **20** 495, 1875.

<sup>23</sup> Coates, V., and Coombs, C. F. *Observations on the Rheumatic Nodule*, *Arch Dis Childhood* **1** 183, 1926.

Not many observations have been reported concerning the frequency and structure of subcutaneous nodules in patients having chronic arthritis. Hawthorne<sup>24a</sup> described subcutaneous nodules in 6 patients, and he considered rheumatic fever and rheumatoid arthritis as different manifestations of the same process. Garrod<sup>6</sup> also observed subcutaneous nodules in chronic arthritis. Wick<sup>25</sup> saw a relationship between the nodules found in chronic arthritis and those seen in acute rheumatic fever. Subcutaneous nodules in cases of chronic arthritis were also described by Coates and Coombs,<sup>23</sup> Freund,<sup>26</sup> and Dawson and Boots<sup>24b</sup>

In this series, 300 consecutive patients with chronic arthritis were examined for subcutaneous nodules. The nodules were studied with respect to frequency, location, size, shape, consistence, development and duration. Nodules from 20 patients were removed and examined grossly and microscopically. A portion of each nodule was also cultured for bacterial growth.

Dawson and Boots found that the incidence of subcutaneous nodules in 200 consecutive cases of arthritis was about 20 per cent. Cecil referred to them as being present in from 3 to 4 per cent of the cases.

In our series of 300 patients with chronic arthritis, subcutaneous nodules were found in 94 (31.3 per cent). No attempt was made to determine the frequency of such nodules in any special class of conditions, as I have been unable to recognize distinct divisions, such as rheumatoid arthritis (atrophic, proliferative) and osteo-arthritis (hypertrophic, degenerative). The ages of patients with nodules was determined, and there was a very high incidence of involvement in the older age groups, 54 of the 94 persons with nodules being 50 years of age or more. The condition in many of these older persons would fit the criteria advanced for osteo-arthritis.

The cases in which nodules were found did not fall in any definite group and could not be distinguished in any way from a large number of cases of arthritis without nodules.

Patients were frequently unaware of the presence of nodules, however, in some cases they were painful, especially those located on the plantar surfaces of the feet.

In most cases it is difficult to determine the duration of the nodules. In some instances they were known to have been present for from a

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24 (a) Hawthorne, C. O. *Rheumatism, Rheumatoid Arthritis and Subcutaneous Nodules*, London, J. & A. Churchill, 1900, (b) cited by Dawson, M. H., and Boots, R. H. *Subcutaneous Nodules in Rheumatoid (Chronic Infectious) Arthritis*, J. A. M. A. **95** 1894 (Dec. 20) 1930.

25 Wick, L. *Ein Fall von primären chronischen Gelenkrheumatismus mit subcutanen Knoten*, Wien med. Wchnschr. **31** 1804, 1910.

26 Freund, E. *Ueber rheumatische Knoten bei chronischer Polyarthritits*, Wien Arch. f. inn. Med. **16** 73, 1928.

few months to as long as fifteen years. In general, it has seemed that nodules were of shorter duration in younger persons.

They were distributed chiefly over the extremities, more frequently on the upper extremities than the lower ones. In 5 patients there were nodules over the sacro-iliac joints. There was a frequent tendency toward bilateral distribution. In 94 patients nodules were found in 127 locations, excluding bilateral symmetrical involvement.

The nodules varied in size from 5 mm or less to 3 cm. All were movable and not attached to the skin, but some were rather firmly adherent to the underlying tissues. Many of the larger nodules were cystic and contained disconnected masses of tissue. The nodules were grossly similar to those occasionally occurring in syphilis, which are referred to as juxta-articular nodules. The experience of my colleagues and myself in a series of patients in the outpatient department has indicated that such nodules are only rarely found in syphilis.

The microscopic appearance of the tissues was studied by Clawson<sup>101</sup> and found to be chiefly polyblastic in character and similar to the reactions found in subcutaneous nodules and in heart valves in acute rheumatic fever, in the heart valves in subacute rheumatic endocarditis, and in subcutaneous nodules produced experimentally in rabbits by the injection of streptococci. Cultures of the nodules were taken in 17 cases, and streptococci were recovered in 12 instances (70.6 per cent).

#### ROENTGEN FINDINGS IN ARTHRITIS

Roentgen study has been of much value in determining certain types of changes in the joints which may be present in arthritis, especially destruction of cartilage and bone, atrophy of the bone and the production of new bone. Such study, however, has led to some confusion in diagnosis, as changes in the joints due to various etiologic agents may at times simulate each other, and cases have often been placed in the same class without consideration of the underlying cause. Roentgen study in certain severe clinical types of arthritis also shows little or no change, such is the case in the severe periarticular involvement often seen in children and young adults. Often the diagnosis of the type of arthritis present is withheld until the report on the roentgen examination is available, and then the diagnosis is made according to the change seen in the roentgenogram. The terminology most in use by roentgenologists is that employed in Goldthwait's classification, namely, infectious, atrophic and hypertrophic arthritis. The prominent change in atrophic arthritis was said to be atrophy of the bones adjacent to joints, associated with the destruction of cartilage. Goldthwait expressed the belief that the formation of spicules was indicative of a separate type termed infectious arthritis, although atrophy of the bones and destruction of

cartilage were also said to be prominent in such cases. The characteristic changes in hypertrophic arthritis were said to be formation of new bone, such as lipping, with moderate or little destruction of cartilage and little or no destruction of bone.

There are on record some cases in which roentgenograms have been taken early in the process and the condition classified as atrophic arthritis, and in which a diagnosis of hypertrophic or mixed arthritis has been made later. In considering the roentgen changes, the duration of the lesion and the age of the patient are apparently two important factors. Younger persons frequently have arthritic involvement with negative roentgen findings, while in older persons the roentgen findings are often out of proportion to the symptoms present. The formation of new bone probably represents a rather advanced result of arthritis and may be simulated by other types of change, such as traumatic conditions of the joints in which the destruction of cartilage has taken place, with the subsequent formation of new bone. Senescent changes likewise may simulate true arthritic changes, although such changes in general are apt to be more symmetrical and chiefly present in the spine. The clinical history also is an aid in differentiating such cases from those of true arthritis.

In general, it can be said that the arbitrary selection of one joint for roentgen study and diagnosis of the type of arthritis, is an incomplete method and has led to many errors in classification. With this point in mind, 60 unselected consecutive arthritic patients were thoroughly studied by Dr. Rigler, roentgenologist of the University of Minnesota Hospital. A roentgenogram was made of every joint in which pain was or had been present, and the duration of the involvement was recorded. From this study, it was found that a majority of cases showed more than one accepted type of roentgen change, according to the Goldthwait classification, and that it was possible only to state the type of changes present and the joints involved. Only 33.3 per cent of the patients showed a single type of accepted roentgen change according to the Goldthwait classification, 58.3 per cent showed mixed changes, and 8.3 per cent, none.

Another common source of error in the selection of one or two joints for roentgen examination is that in certain joints, such as the shoulder, so-called atrophic changes are present in nearly all cases, while in such a joint as the knee, hypertrophic changes are much more commonly present. This is particularly significant when one considers that involvement of the knees and shoulders is present in arthritic persons of all age groups in about the same incidence. While roentgen study helps in distinguishing arthritis of streptococcic, gonococcic, tuberculous and syphilitic origin, one cannot make positive etiologic diagnoses in many

cases, and there may be various manifestations of any type of the condition. From an etiologic standpoint, however, the majority of cases seem to be due to streptococcic infection, in general, such a type often tends to involve multiple joints, with varied roentgenographic manifestations. The age of the patient, the duration of symptoms and the joint shown in the roentgenogram are important factors in determining the roentgen changes present in cases of streptococcic arthritis.

#### PREVIOUS THERAPY

A study has been made of the previous treatment received by the patients in this group. Special attention has been paid to the results of the removal of alleged foci of infection, especially teeth, tonsils and sinuses. A high percentage of patients had received such treatment, and in only a few instances was it followed by much clinical improvement. In many of these cases there was little or no clinical correlation between the arthritis and the possible focus removed. In practically no case of well established or long-standing arthritis was there any improvement following such treatment. This is not difficult to understand when one considers the fact that in such cases the streptococci are probably already well established in the tissues of the joints and in the subcutaneous nodules, which in themselves are sufficient locations for the continuance and further spread of the arthritic infection. It is obvious from the histories alone that this probably occurs in cases of chronic arthritis persisting for years which often follow acute transitory infections. In patients who have had a recent onset of articular symptoms or recurrent symptoms, the results from the removal of supposed foci have been more encouraging, however, in such conditions there is frequently subsidence of symptoms without treatment. In a patient who had not had previous articular symptoms, chronic arthritis developed immediately after tonsillectomy. In several other patients there was a marked aggravation of the symptoms following tonsillectomy or extraction of teeth.

Typhoid vaccine had been administered intravenously to about 60 patients previously, it was found to be of no value in almost every case. A few of the patients so treated reported feeling better for one or two days following the injection, and one patient reported improvement of several months' duration.

The majority of patients had received medication and various forms of physical therapy, with temporary relief in some cases, but in nearly every case without any permanent change in the course of the disease.

Dietary treatments of all types had been tried in many cases, chiefly diets low in carbohydrates, though in other cases diets low in proteins and other special types of diets had been used. Little definite improvement from dietary management alone was reported.



It is difficult to associate arthritis definitely with chronic diseases. The relationship to other infections of streptococcic origin seems clearly established on a clinical basis. Psoriasis is mentioned as being frequently associated with arthritis, and it was found to be present in 5 of 350 cases (1.4 per cent) in our series. Histories of pleurisy and chronic bronchitis were not infrequent, but it was not determined whether such conditions were of greater frequency than in a control group.

#### LABORATORY DATA

*Studies on the Blood*—The blood of 100 consecutive arthritic patients was studied. This study included the hemoglobin determinations and counts of the white and red cells and differential and morphologic studies.

The hemoglobin was less than 70 per cent in 15 per cent of the patients, the incidence of such low readings was significantly greater than was found in the total dispensary group. In 10,000 consecutive dispensary patients, excluding pregnant women, there was an incidence of about 3 per cent with less than 70 per cent hemoglobin. In all cases the hemoglobin has been measured by the same method, with a corrected Sahli hemoglobinometer. The red cell count has not been reduced in proportion to the hemoglobin, and, in general, a low index for hemoglobin was present. There was a more frequent occurrence of moderate leukocytosis in the arthritic patients than in a control series.

Morphologic studies have shown little or no significant changes in either the red or the white cells. Moderate evidences of toxicity in the neutrophils have been manifested in a number of cases, but not in a significant manner.

Wassermann tests of the blood have been made for all patients, and the reaction was found to be positive in very few cases.

*Urinalysis*—Urinalysis has been made as a routine in all cases, no significant observations were made which could distinguish the arthritic group from any general group. Diabetes was present in only 3 of the 350 patients in the arthritic group. Transitory glycosuria was not found frequently in this group.

#### SUMMARY

The analysis has covered a number of clinical phases of arthritis. The sex incidence and age at onset have been determined. The frequency and severity of involvement of individual joints have been tabulated. The clinical relationship of rheumatic fever and chronic arthritis has been considered and a study made of the incidence of organic heart disease in the latter condition. A study has been made of streptococcic infections and trauma as inciting factors in chronic

arthritis The frequency and distribution of subcutaneous nodules have been determined The significance of roentgen studies has been discussed Previous therapeutic methods and results have been reviewed, and a summary of the results of studies of the blood has been made

A number of persons with transitory pains in the muscles and joints have been omitted from consideration because the study has been limited to patients with symptoms of at least two months' duration Temporary involvement of various degrees has been observed frequently in persons in the age group from 15 to 30 years Many cases in which the condition is difficult to class definitely as rheumatic fever or as chronic arthritis occur in these ages It is my opinion that no sharp line of clinical distinction exists between these conditions at any age, although there are marked clinical differences in selected cases, just as there are marked clinical differences among cases termed chronic arthritis On the basis of the clinical and the etiologic evidence, it seems likely that streptococcic infection is responsible for the majority of acute and chronic infections of the joints, such as rheumatic fever, rheumatoid arthritis (atrophic, proliferative) and osteo-arthritis (hypertrophic, degenerative) Cases to be excepted from the preceding statement are conditions such as senescent, traumatic and posthemorrhagic changes, which are frequently included under osteo-arthritis It is to be hoped that an acceptable etiologic classification will be adopted in the near future

#### CONCLUSIONS

1 Three hundred and fifty consecutive cases of chronic arthritis have been subjected to a clinical analysis In this series, 68.57 per cent of the patients were women and 31.43 per cent were men The peak of onset occurred in the fifth decade for both sexes The duration of symptoms in this series was over one year in 88 per cent and over five years in 55 per cent of the cases

2 Monarticular involvement, in a strict sense, was present in only 5 of the 350 cases A study of the joints involved showed the knees to be affected most frequently in 82.8 per cent of all cases Other joints commonly involved were the following fingers, 61.1 per cent, ankles, 58.3 per cent, spine, 57.1 per cent, shoulders, 57.1 per cent, wrists, 50 per cent, hips, 44.6 per cent, and elbows, 42.6 per cent

3 There are certain definite sex differences in the distribution of the joints affected, there being a significantly more frequent involvement of the fingers, hands, and toes in women and of the spine, hips and feet in men There is also a marked difference between the sexes in the joints most severely involved, the fingers being the most seriously affected in 16.6 per cent of the women and in only 0.9 per cent of the

men, while, on the other hand, the spine was most severely affected in 20 per cent of the men and in only 5.8 per cent of the women

4 A study made of the percentage distribution of involvement of the joints by decades showed no striking differences in the distribution in arthritis coming on at different decades of life

5 In 32 patients with chronic arthritis there was an acute febrile onset which was similar to the clinical description of rheumatic fever. Such an acute onset was much more frequent in the younger age group. Of this number, 6 (18.7 per cent) had definite rheumatic involvement of the heart. The incidence of rheumatic disease of the heart in the total group of 350 patients was 7 (2 per cent)

6 Probable sources of streptococcic infection were known to precede the arthritis in 102 cases (29.1 per cent). The more common inciting sources were dental infection, sinusitis, acute respiratory infection, tonsillitis, puerperal sepsis and the puerperium without known infection. Polyarthritis immediately followed definite trauma in 12 cases

7 Subcutaneous nodules were sought for in 300 consecutive arthritic patients and were found to be present in 94 cases (31.3 per cent). The incidence of subcutaneous nodules was determined for the various age groups, they were found to be present in over 40 per cent of the patients over 50 years of age. Such nodules were found in patients with various clinical and roentgen findings

8 Roentgen examinations of all painful joints in 60 consecutive cases have shown a pure type of involvement in only 33.3 per cent, a mixed type in 58.3 per cent and no positive findings in 8.3 per cent of the cases

# EXOGENOUS TUBERCULOUS INFECTION OF ADULTS

## MARITAL TUBERCULOSIS

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The susceptibility of adults to the contagion of tuberculosis, a classic subject of controversy, is still under discussion. The disease, many have maintained, does not occur more frequently in adults conspicuously exposed to the disease than in the general population. Statistics from sanatoriums and hospitals for the treatment of tuberculosis have been cited to show that tuberculosis is not unusually frequent in doctors and nurses in constant contact with it. However, in these institutions, suitable precautions, it is true, may be effective in preventing spread of infection. Those who deny the occurrence of exogenous infection of adults base their belief chiefly on the supposed infrequency of obvious marital contagion. If husbands or wives fail to acquire the disease when their consorts suffer with it, there is scant probability that adults are susceptible to infection from without.

Study of the pathologic anatomy has convinced many observers that tuberculosis of adolescence and adult life is a new infection modified by the combination of immunity and hypersusceptibility which follows a first infection acquired, with few exceptions, between infancy and adolescence.

The literature on tuberculosis contains data for an immense collection of statistics concerning marital tuberculosis, in great part based on the histories of parents of persons with tuberculosis. Pearson, in analyzing the histories of 40,000 couples assembled by Pope<sup>1</sup> from the literature on the subject, found scant evidence of marital infection, whereas Arnould,<sup>2</sup> somewhat later, collecting the histories of 53,000 couples, found some evidence of transmission from one consort to another. Nearly every year new studies with varying results are published.

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From the Henry Phipps Institute, University of Pennsylvania

1 Pope, E G, and Pearson, K. Drapers' Company Research Memoirs III Marital Infection, Department of Applied Mathematics, University College, University of London, 1908

2 Arnould, E. Rev de la tuberc 6:177, 1925

The data contained in this paper are published because (1) they are, with few exceptions, the result of direct observation of married couples continued with varying completeness during periods up to eight years, (2) the studies were conducted with the aid of roentgenologic methods that increase the frequency and accuracy with which pulmonary tuberculosis can be recognized and defined, and (3) the data include observations on latent lesions which, being unaccompanied by significant symptoms or physical signs, preclude the selective examination of those affected

With the effective application to the examination of the chest of the roentgenologic methods developed in the last decade, the aspect of the problem has wholly changed. It is now possible to recognize pulmonary tuberculosis accompanied by manifest symptoms and physical signs with an accuracy previously impossible, and the scope of such

TABLE 1—*Occurrence of Clinically Manifest Tuberculosis in White Wives and Husbands After Its Appearance in the Other Marital Partner*

	Number Exposed	Number Not Exam- ined	Number with Tuber- culosis	Per Cent with Tuberculosis with Probable Error
Wives exposed to husbands having tuberculosis with Tubercle bacilli in sputum	145	45	18	12.4 $\pm$ 1.85
No tubercle bacilli in sputum	89	33	4	4.5 $\pm$ 1.48
Husbands exposed to wives having tuberculosis with Tubercle bacilli in sputum	70	37	9	12.9 $\pm$ 2.70
No tubercle bacilli in sputum	72	47	6	8.3 $\pm$ 2.19

observations is widely extended by the recognition of lesions unaccompanied by significant symptoms or physical signs and hence designated latent

The number of married couples studied of whom one or both consorts suffered with tuberculosis was 533, 366 were white (table 1) and 157, Negro (table 7). Since carefully prepared clinical histories were available, it was possible to determine in which marital partner the disease first developed and whether the sputum of this person was known to have contained tubercle bacilli.

When the husband first suffered from pulmonary tuberculosis and had tubercle bacilli in his sputum, tuberculosis appeared in the wife in 12.4 per cent of the cases. When wives first had the disease, manifest pulmonary tuberculosis appeared later in 12.9 per cent of their husbands. It is, then, known to have occurred with approximately equal frequency in husband or wife when the other partner suffered with open tuberculosis.

When the sputum of the person who first became sick with tuberculosis contained no tubercle bacilli at the time when it was examined the incidence of the disease in the marital partner was significantly less, being 4.5 per cent in exposed wives and 8.3 per cent in exposed hus-

bands There is no reason to doubt that at some time during the association of these husbands and wives tubercle bacilli were discharged in the sputum

The foregoing figures concerning the incidence of conjugal tuberculosis show how many partners are known to have acquired the disease, but they do not exclude the possibility that the actual number is larger Of white wives, for example, 234 were exposed to infection by the husband, but of these 78 were not available for examination, and of white husbands a much smaller number presented themselves for examination, so that of 142, more than half, namely, 84, were not examined It is well recognized that not a few persons with symptoms of pulmonary tuberculosis shun examination because they dread being told that they have tuberculosis Had it been possible to examine all of these

TABLE 2—*Occurrence of Latent Apical Tuberculosis in White Wives and Husbands After the Appearance of Tuberculosis in the Other Marital Partner*

	Number Examined and Found to Have No Clin- ically Manifest Tuberculosis	Number with Latent Apical Tuberculosis	Per Cent with Latent Apical Tuberculosis
Wives exposed to husbands having tuberculosis with Tubercle bacilli in sputum	82	21	25.6
No tubercle bacilli in sputum	52	10	19.2
Husbands exposed to wives having tuberculosis with Tubercle bacilli in sputum	24	9	27.5
No tubercle bacilli in sputum	19	6	31.6

persons, additional instances of the disease would have been discovered, and the figure representing its incidence would have been increased

Since latent tuberculosis is unaccompanied by symptoms and unrecognizable by the patient, those with this lesion are no more likely to come to the dispensary for examination than are other persons who have been in contact with tuberculosis Hence the percentage of latent apical lesions obtained by examination of exposed marital partners with no manifest tuberculosis is equally applicable to those who have failed to report for examination

Table 2 gives the incidence of latent apical tuberculosis in those wives or husbands who had been exposed to partners with clinically manifest tuberculosis This enumeration necessarily excludes the exposed partners who had passed through a period of latency and developed clinically manifest tuberculosis

The latent apical lesions enumerated in table 2 have been classified in table 3 as follows Group I Definite but scant lesions recognized immediately below the second rib on one or both sides Group II Well defined lesions of which the extent approximates or exceeds half of the apical area above the clavicle Group III Lesions that extend below the

clavicle and fall within the definition applied to minimal tuberculosis when the disease is manifest. These lesions are limited to the area above the level of the second chondrosternal junction in front and the fifth vertebral spine behind. When the lesion is densely infiltrated or there is a cavity, it is regarded as a moderately advanced latent lesion and placed in group IV. Group IV. Lesions that exceed those of group III, as defined, in extent or severity, and are commonly classified as moderately advanced when clinically manifest.

It is noteworthy that 7 of 21 lesions in persons exposed to patients with sputum-positive tuberculosis extended below the clavicle, and 2 of these were "moderately advanced," whereas only 3 of 16 lesions in persons exposed to patients with sputum-negative tuberculosis extended below the clavicle, and none of them was moderately advanced.

TABLE 3—*Anatomic Extent of Latent Apical Lesions*

	I	II	III	IV	
	Small Apical Lesions	Lesions Approxi- mating or Exceeding Half Area Above the Clavicle	Apical Lesions Extending Below Clavicle and Not Exceeding Those of Minimal Tuberculosis	Lesions Equivalent to Those of Moderately Advanced Tuberculosis	Total
In wives exposed to					
Sputum positive tuberculosis	10	6	3	2	21
Sputum negative tuberculosis	3	5	2		10
In husbands exposed to					
Sputum positive tuberculosis	4	3	2		9
Sputum negative tuberculosis	2	3	1		6

Latent apical tuberculosis, like clinically manifest tuberculosis, was more frequent in husbands than in wives exposed to the disease (table 2). As with manifest pulmonary disease, the relation of the latent apical lesion to infection is shown by its greater frequency and severity in persons exposed to partners with tubercle bacilli in the sputum than in those whose partners were not known to have had tubercle bacilli in the sputum (table 3). Nevertheless, when the results of examination of the sputum were negative the presence of tubercle bacilli in the sputum obviously cannot be excluded, because the number of examinations varied widely, and it is probable that tubercle bacilli were present in some instances before the period of our observation.

During the course of the present study husbands and wives in 108 families in which tuberculosis was not known to exist were examined, with the results shown in table 4.

Of the 5 latent apical lesions in wives, 2 were in group I, 2 in group II and 1 in group III. The latent lesion found in a husband fell in group II.

Comparison of tables 2 and 4 shows that latent apical tuberculosis is far more common in marital partners exposed to tuberculosis than in those with no known contact with the disease. A general summary of the observations that we have made on latent apical tuberculosis is given in table 5. The probability that this is a chance difference is 0.00023 in 100, or approximately 1 to 500,000.<sup>3</sup>

Of 145 wives exposed to open tuberculosis in the husband 18 (table 1) had clinically manifest tuberculosis, which leaves 127, of whom 82 were examined by means of roentgenographic films of the chest. Of this number 21, or 25.6 per cent (table 2), were found to have latent apical tuberculosis. There is no reason to doubt that latent apical

TABLE 4—*Occurrence of Latent Apical Tuberculosis in White Wives and Husbands with No Known Contact with Tuberculosis*

	Number Examined	Number with Latent Apical Tuberculosis	Per Cent with Latent Apical Tuberculosis
Wives	95	5	5.3
Husbands	47	1	2.1
Total	142	6	4.2

TABLE 5—*Persons with Latent Apical Tuberculosis*

	Number Examined	Number with Latent Apical Tuberculosis	Per Cent with Latent Apical Tuberculosis and Probable Error
Exposed to tuberculosis in husband or wife	177	46	25.99 $\pm$ 2.22
With no known exposure to tuberculosis	142	6	4.23 $\pm$ 1.92

tuberculosis and perhaps manifest tuberculosis in addition occurred in at least an equal percentage of those that were not examined, namely, in 25.6 per cent of 45, or 11. The total number of those who may be assumed to have had latent apical tuberculous lesions is 32, or 35.5 per cent. The same estimate applied to other figures of tables 1 and 2 gives the results shown in table 6.

It is commonly assumed that the incidence of clinically recognizable tuberculosis in the general population is approximately 1 per cent, that of latent apical tuberculosis in husbands and wives with no familial contact with tuberculosis was 4.2 per cent (table 4). Hence the frequency of adult types of tuberculous infection in those exposed to the disease by marital contact as shown by the figures in table 6 is comparable to an incidence of approximately 5 per cent in husbands and wives with no known familial contact with tuberculosis.

<sup>3</sup> Miss Marjorie Gooch made this estimate.



Table 7 shows the frequency with which calcified lesions of a first infection occur as recognizable nodules in lungs or tracheobronchial lymph nodes of wives and husbands exposed to marital contact with tuberculosis. It is noteworthy that roentgenographic films reveal only

TABLE 6—*Incidence of Adult Type of Tuberculosis Infection in Wives or Husbands After the Appearance of Clinically Manifest Tuberculosis in Other Marital Partner*

	Per Cent with Manifest Tuber- culosis	Estimated per Cent with Latent Apical Tuber- culosis	Estimated per Cent with Both Forms of Tuber- culosis
Wives in contact with husbands having tuberculosis with			
Tubercle bacilli in sputum	12.4	23.1	35.5
No tubercle bacilli in sputum	4.5	18.4	22.9
Husbands in contact with wives having tuberculosis with			
Tubercle bacilli in sputum	12.9	32.7	45.6
No tubercle bacilli in sputum	8.3	27.6	35.9

TABLE 7—*Incidence of Calcified Lesions of First Infection Found in Lungs and Tracheobronchial Lymph Nodes of Wives or Husbands*

	Number Examined	Lesions of First Infection Found	Per Cent of Lesions of First Infection Found
Wives in contact with husbands having tuberculosis with			
Tubercle bacilli in sputum	82	27	32.9
No tubercle bacilli in sputum	52	10	17.2
Wives with no known contact with tuberculosis	95	21	22.1
Husbands in contact with wives having tuberculosis with			
Tubercle bacilli in sputum	24	5	20.8
No tubercle bacilli in sputum	19	2	10.6
Husbands with no known contact with tuberculosis	47	9	19.2

TABLE 8—*Occurrence of Clinically Manifest and Latent Apical Tuberculosis in Negro Wives or Husbands After Its Appearance in the Other Marital Partner*

	Number Exposed	Number with Manifest Tuber- culosis	Number with No Manifest Tuber- culosis That Were Examined	Number with Latent Apical Tuber- culosis
Wives in contact with husband having tuberculosis with				
Tubercle bacilli in sputum	79	2	24	2
No tubercle bacilli in sputum	21	0	4	0
Husbands in contact with wives having tuberculosis with				
Tubercle bacilli in sputum	51	2	18	2
No tubercle bacilli in sputum	5	1	3	1

a part of the calcified lesions of the childhood type demonstrable in lungs examined at autopsy (Miller<sup>4</sup>).

These figures, which are very small in some of the groups, suggest that marital contact with tuberculosis may perhaps increase the frequency of lesions of first infection, but the preponderance of infection with marital contact on the one hand and with no known familial association with tuberculosis on the other is far less than in adult types of infection in the corresponding groups of married persons.

The number of married couples of the Negro race under observation has been too small to give satisfactory information concerning the incidence of tuberculosis in the marital partners of tuberculous persons of this race. It has been possible to follow few families continuously, and men especially fail to seek medical care until their disease is advanced. The figures in table 8 are cited in order to show the difficulty of collecting under unfavorable conditions information concerning marital tuberculosis.

Of the latent apical lesions found in wives, one was represented by a scant shadow occupying approximately half of the apex above the clavicle (group II) and the other extended from above below the clavicle (group III). Of the latent apical lesions of husbands, 2 were represented by scant shadows below the second rib (group I) and 1 extended from above below the clavicle (group III).

#### CONCLUSIONS

When roentgenographic methods are used for the recognition of tuberculous lesions of the lungs in husbands and wives in contact with a tuberculous partner, exogenous infection of adults is clearly demonstrable.

Husbands and wives in marital contact with tuberculosis under varying conditions are infected from five to nine times as often as persons with no known contact with the disease, husbands are infected oftener than wives.

The frequency of infection in wives exposed to husbands with tubercle bacilli in the sputum was 35.5 per cent, in those exposed to husbands with no demonstrable tubercle bacilli, 22.9 per cent. The incidence of infection in husbands exposed to wives with open tuberculosis was 45.6 per cent, and when there were no tubercle bacilli in the sputum it was 35.9 per cent.

When the incidence of latent apical tuberculosis in persons exposed to tuberculosis in husband or wife is compared with that in husbands or wives with no known exposure to tuberculosis, the possibility that the difference has occurred by chance is negligible.

<sup>4</sup> Miller, G. R. *Am J Roentgenol* 36:191, 1931.

# NORMAL RENAL THRESHOLD FOR DEXTROSE

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The results of experiments performed solely to determine, as nearly as clinically possible, the normal renal threshold for dextrose are reported in this paper

Most of the previous information on this subject has been gleaned incidentally during the study of dextrose tolerance curves. A great many of the patients studied were hospital patients. The various values reported led us to attempt to discover the renal threshold in normal persons. We believe that while there are small amounts of reducing substances in the urine most of the time, there is a definite threshold level at which large quantities of dextrose are excreted in the urine. This is shown in numerous cases by an abrupt appearance of heavy precipitate when a series of successive specimens of urine are tested with Benedict's solution while the blood sugar is rising after the ingestion of a large quantity of dextrose.

The normal renal threshold has been variously given in textbooks and papers since Jacobsen's<sup>1</sup> article in 1913. He reported values of from 160 to 170 mg per hundred cubic centimeters, Hamman and Hirschman<sup>2</sup> (1917) and Todd and Sanford<sup>3</sup> (1930) both reported values from 170 to 180 mg, Osgood and Haskins<sup>4</sup> (1931), from 170 to 190 mg, Stitt<sup>5</sup> (1927) and Hawk and Bergeim<sup>6</sup> (1927), from 160 to 180

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1 Jacobsen, A. T. B. Untersuchungen über den Einfluss verschiedener Nahrungsmittel auf den Blutzucker bei normalen, zuckerkranken und graviden Personen, *Biochem. Ztschr.* **56** 471, 1913.

2 Hamman, L., and Hirschman, I. I. Studies on Blood Sugar, *Arch. Int. Med.* **20** 761 (Nov.) 1917.

3 Todd, J. C., and Sanford, A. H. A Textbook of Clinical Diagnosis by Laboratory Methods, Philadelphia, W. B. Saunders Company, 1930, p. 345.

4 Osgood, E. E., and Haskins, H. D. A Textbook of Laboratory Diagnosis, Philadelphia, P. Blakiston's Son & Company, 1931, p. 54.

5 Stitt, E. R. A Textbook of Practical Bacteriology, Blood Work, and Animal Parasitology, Philadelphia, P. Blakiston's Son & Company, 1927, p. 728.

6 Hawk, P. B., and Bergeim, O. A Textbook of Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son & Company, 1927.

mg, and Cummer<sup>7</sup> (1926), over 200 mg. Johns<sup>8</sup> (1930) expressed the belief that all of these values are too high, and that there is "no such thing as a normal threshold, but that for all individuals there is an individual threshold." Eight of the fourteen cases of Goto and Kuno<sup>9</sup> (1921) showed values below 160 mg. Mackay<sup>10</sup> (1927) found cases that did not show glycosuria when the blood sugar was over 200 mg for some time. Glassberg,<sup>11</sup> during studies on arteriovenous blood, found two cases with variable renal thresholds. Additional references only add greater confusion to these figures.

#### METHODS

Many of the variations in values may be accounted for by the use of different methods of determining the blood sugar level. To be sure of the best method of determining the true blood sugar, it was first found that a 10 per cent yeast suspension will remove all the fermentable sugar in fifteen minutes, as stated by Somogyi<sup>12</sup> (1927). The blood sugar of twenty-five normal and dispensary patients was determined on filtrates prepared (1) by the Folin-Wu tungstate precipitating method, (2) by the zinc sulphate-sodium hydroxide method of Somogyi<sup>13</sup> and (3) by tungstate precipitation after fermentation with 10 per cent yeast suspension. The results thus obtained are shown in table 1. The average nonfermentable substance was 21.2 mg per hundred cubic centimeters despite the presence of disease. There was a variation of from 11 to 32 mg per hundred cubic centimeters, 90 per cent of the cases varying from 17 to 28 mg. When the zinc sulphate-sodium hydroxide precipitation method was used, there was a deviation from the true sugar value of  $\pm 7$  mg per hundred cubic centimeters, as shown by the results of the tungstate method minus those of the combined yeast and tungstate method. With this method, the results ranged from 9 to 27 mg lower than with the tungstate method, with an average of 20.2 mg. On the basis of these findings, it was decided to use the zinc sulphate-sodium hydroxide method of precipitating the blood proteins, and, for comparison with most of the older figures, to add to the results 21 mg per hundred cubic centimeters. In this we defer to Somogyi's<sup>14</sup> larger series and avoid splitting milligrams.

To determine the sugar in the filtrate, Haskins and Holbrook's<sup>15</sup> modification of the Shaffer-Hartman method was used.

7 Cummer, C. L. *A Textbook of Clinical Laboratory Methods*, Philadelphia, Lea & Febiger, 1926, p. 254.

8 Johns, H. J. *A Study of One Thousand One Hundred Glucose Tolerance Tests*, M. J. & Rec. **131**: 287, 351 and 398, 1930.

9 Goto, K., and Kuno, N. *Studies on the Renal Threshold for Glucose*, Arch. Int. Med. **27**: 224 (Feb.) 1921.

10 Mackay, H. L. *Observations on the Renal Threshold for Glucose*, Biochem. J. **21**: 760, 1927.

11 Glassberg, B. Y. *Kidney Threshold for Glucose in Diabetic and Non-Diabetic Persons*, J. Lab. & Clin. Med. **16**: 948, 1931.

12 Somogyi, M. *The Reducing Non-Sugars and True Sugar in Human Blood*, J. Biol. Chem. **75**: 33, 1927.

13 Somogyi, M. *A Method for the Preparation of Blood Filtrates for the Determination of Sugar*, J. Biol. Chem. **86**: 655, 1930.

14 Somogyi, M. *The Nature of Blood Sugar*, J. Biol. Chem. **80**: 733, 1928.

15 Osgood, E. E., and Haskins, H. D. *A Textbook of Laboratory Diagnosis*, Philadelphia, P. Blakiston's Son & Company, 1931, pp. 291 and 263.

## EXPERIMENTS

Healthy male medical students between the ages of 20 and 32 were used. In none of these had glycosuria been detected previously.

1 Varying amounts of dextrose were given, starting with 150 Gm in a 50 per cent solution and increasing to 300 Gm. In five of six subjects who were given 300 Gm, positive results were obtained, but since one subject suffered a gastric hemorrhage, the amount was reduced to 250 Gm, and no more accidents occurred.

2 After the dextrose was given, the subject was asked to urinate every five minutes. A control specimen taken before the experiment and those taken during

TABLE 1—*A Comparison of the Tungstate, Zinc Sulphate-Sodium Hydroxide and a Combination of the Yeast and Tungstate Methods for Determining Blood Sugar*

Number	Tungstate Method, Mg per 100 Cc	Yeast Plus Tungstate, Mg per 100 Cc	True Sugar, Mg per 100 Cc	Zinc Sulphate Sodium Hydroxide Method, Mg per 100 Cc	Deviation of Zinc Sulphate Sodium Hydroxide from True Sugar, Mg	Red Cell Count	Source
1	127	19	108	112	+4	1,910,000	M C H *
2	112	11	101	103	+2	2,950,000	M C H
3	80	17	63	65	+2	3,250,000	Clinic
4	97	17	80	73	-7	4,000,000	Clinic
5	88	19	69	69	0	4,100,000	Clinic
6	123	24	99	104	+5	4,520,000	Clinic
7	99	18	81	78	-3	4,560,000	Clinic
8	88	19	69	68	-1	4,800,000	Clinic
9	87	20	67	70	+3	4,900,000	Clinic
10	70	21	49	48	-1	5,100,000	Clinic
11	104	17	87	87	0	5,550,000	Clinic
12	109	28	81	83	+2	5,840,000	Clinic
13	85	20	65	72	+7	6,650,000	Clinic
14	123	32	91	96	+5	Not determined	Clinic
15	99	21	78	76	-2	Not determined	Clinic
16	282	25	257	257	0	Not determined	Clinic
17	90	24	66	65	-1	Not determined	Clinic
18	77	21	56	59	+3	Not determined	Clinic
19	117	23	94	98	+4	Not determined	Clinic
20	153	22	136	138	+2	Not determined	Clinic
21	114	20	94	87	-7	Not determined	Clinic
22	98	22	76	78	+2	Normal	
23	95	25	70	76	+6	Normal	
24	89	24	65	66	+1	Normal	
25	99	22	77	77	0	Normal	
Average		21.2			+1		
Variation		11 to 32			-7 to +7		

\* Multnomah County Hospital

it were boiled for two minutes in Benedict's solution directly over a flame. When the test became faintly positive, venous blood was drawn. The time elapsing between urination and the completed withdrawal of the blood averaged about five minutes. The time required for the urine to reach the bladder could not be measured.

3 In several cases that did not show glycosuria, blood was drawn at thirty and forty-five minutes to determine the maximum blood sugar level attained.

4 No special preparation by the subject was required. He was advised to drink a great deal of water before the experiment. Most of the tests were made at noon. Only four patients were unable to urinate as required, and no blood was taken from them. Urination in a few of the others was somewhat irregular, but unless the urine five minutes preceding the final positive specimen was negative, the results were not used.

# RESULTS

Thirty-four persons were tested, four could not urinate, eight did not have glycosuria, and twenty-two gave satisfactory results. Three of those who did not have glycosuria were given a larger amount of dextrose, and two then excreted sugar, making a total of twenty-four satisfactory tests. In five cases in which the threshold had been established,

TABLE 2—Renal Threshold for Dextrose in Twenty-Four Normal Subjects

Number	Dextrose Given, Gm	True Sugar,* Mg per 100 Cc	Estimated† Tungstate Value, Mg per 100 Cc	Minutes
1	250	99	120	35
1	250	122	143	35
2	250	117	138	30
2	250	137	158	30
3	250	123	144	35
4	250	134	155	35
4	250	No glycosuria		
5	250	142	163	35
6	150	146	167	20
6	150	131	152	35
7	250	146	167	35
8	300	148	169	30
9	150	151	172	30
10	300	151	172	40
11	300	151	172	45
12	300	151	172	30
13	150	152	173	25
13	150	No glycosuria		
14	200	157	178	30
15	250	158	179	35
16	250	158	179	25
17	200	160	181	30
18	250	167	188	35
19	250	168	189	35
20	300	172	193	35
21	250	180	201	30
22	250	180	201	40
23	275	188	209	45
24	250	228	249	30
Average		155.3	175.3	33
Mean		151 to 152	172 to 173	35
Range		99 to 228	120 to 249	20 to 45

\* Determined by zinc sulphate sodium hydroxide method

† Estimated by the addition of 21 mg. to the true sugar values

tests were repeated with the same amount of dextrose, only three of these again showed glycosuria. Table 2 gives the threshold values as obtained, from the lowest to the highest.

For the sake of clarity and brevity, the true figure for sugar will first be given, followed in parenthesis by the estimated value of the tungstate precipitation method. The lowest threshold for sugar found was 99 (120) mg per hundred cubic centimeters, and the highest, 228 (249) mg. The arithmetical average was 155 (176) mg, and the mean, from

151 to 152 (172 to 173) mg. The values in 80 per cent of the cases fell between 140 (160) mg and 190 (210) mg per hundred cubic centimeters. The threshold for one subject was found to vary as much as 23 mg per hundred cubic centimeters. Two others showed variations rather large to be accounted for by experimental error.

The results in six of the eight cases not showing glycosuria, but in which samples of blood were again taken thirty and forty-five minutes after the initial withdrawal of venous blood, are shown in table 3.

The purpose of this table is to show the maximum blood sugar level attained without glycosuria and to give some indication of the reaction of healthy persons to large quantities of dextrose. In every case but one the blood sugar level was definitely lowered after forty-five minutes, but in this case it had not yet risen above 100 mg per hundred cubic centimeters at the end of this period.

TABLE 3—*True Blood Sugar Values of Subjects Without Glycosuria*

Number	Dextrose Ingested, Gm	30 Minutes	45 Minutes
25	200	117	76
26	280	156	134
27	260	153	132
28	270	161	133
29	250	134	106
30	250	82	99

#### COMMENT

While this series is not as large as we should like, it clearly shows that there is a marked variation in the normal renal threshold for dextrose, and that the threshold varies in the same person. Values in a small series of five or six subjects might easily range below or above the figures quoted here. Also, if one were to use tungstate as the precipitating agent and the Shaftei-Haitman titration method, the threshold would appear 21 mg per hundred cubic centimeters higher than the true figures for dextrose. Methods yielding results between those of the methods used here and the older, more inaccurate methods have added still greater confusion to the literature.

Of the four cases with thresholds below 140 (160) mg, it may be said that in each, several twenty-four hour urines were tested and none gave reduction. In this test, 250 Gm of dextrose was needed by three subjects to raise the blood sugar level sufficiently to cause glycosuria, even though their thresholds appeared much lower than normal. It seems from this that something more than a mere lowered threshold is present in renal glycosuria, and that some persons have a compensatory mechanism that enables them to utilize dextrose so that its content in the blood never rises high enough for excretion in the urine.

In two cases in which the experiment was repeated with an added amount of dextrose and in which glycosuria showed on the second test

samples of blood had been taken during the previous test. In one, the blood sugar was 139 mg per hundred cubic centimeters, with no glycosuria. When the renal threshold was determined, it was 148 mg. In the other subject, the first sample was 128 mg, and the threshold was 134 mg per hundred cubic centimeters. This tends to indicate that in these cases the threshold was at a definite level, and that an accurate estimation was obtained.

When Benedict's solution and urine are boiled directly over a flame, a sediment frequently collects that makes detection of a yellow precipitate difficult. In several doubtful cases the sugar in the urine was determined by the Shaffer-Hartman method, and unless there were total reducing substances equivalent to 0.3 Gm or more of dextrose per hundred cubic centimeters of urine, the tests were not considered positive.

The probable error calculated for this series is 15.5 mg. Three times this value either side of the mean should include 95 per cent of all possible cases, as should any stated normal range. This would give a variation of 47 mg from the mean, or a range from 105 to 200 (125 to 220) mg per hundred cubic centimeters. Careful scrutiny of the results in table 2 will show that most of the results are grouped about the mean, that the mean is the most frequently occurring figure, and that the series falls within these limits except in two cases. A series presenting these characteristics should be representative of results to be obtained from a larger series.

#### SUMMARY

1 Filtrates obtained by Somogyi's zinc sulphate-sodium hydroxide method of precipitating blood proteins give true sugar values within a range of  $\pm 7$  mg per hundred cubic centimeters.

2 Filtrates obtained by the tungstate precipitation method give results within a narrow range, averaging 21 mg higher than the true sugar, hence, tungstate methods are clinically satisfactory, and this factor, 21 mg, can be used to transpose results from one method to the other.

3 It seems to be impossible to produce an alimentary glycosuria in some normal persons by the ingestion of large amounts of dextrose.

4 The renal threshold for true sugar varies from 99 to 228 mg per hundred cubic centimeters, 80 per cent of cases having values that range from 140 to 190 mg.

5 If a normal renal threshold is to be given, it must allow for wide variation. We suggest, from the probable error of 15.5 mg and the mean of 151 mg of this series, a probable range of from 105 to 200 mg for true sugar, or from 125 to 220 mg if the tungstate precipitation method is used.



# Book Reviews

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**Blood Sugar in Normal and Sick Children with Special Reference to Coeliac Disease** By Elisabeth Svendsgaard *Acta pædiatrica*, volume 12, supplement 4, 1931

This rather lengthy dissertation on blood sugar values is prepared in three parts. The first deals with the reports in the literature concerning blood sugar values in normal adults, which have been determined by various authors and with various methods. The author points out that these values are not constant from day to day or from hour to hour, and that there may be slight variations due to emotions and physical exertion.

Alimentary hyperglycemia in adults has been studied for the most part by the administration of from 1 to 2 Gm of dextrose per kilogram of body weight. This results in a maximal blood sugar value at from one-half to one hour, the figures ranging from 0.13 to 0.18 per cent. This rise subsides within the following two and a half hours, and any rise remaining after three hours is considered pathologic. There may be a subsequent hypoglycemia with blood sugar values as low as 0.05 per cent below fasting values.

Some authors report a slight variation from the fifth to the ninth decade of life. A preceding diet that is high in protein and fat and low in carbohydrate lowers the tolerance for subsequent carbohydrate, that is, a higher and more protracted hyperglycemia occurs.

A prolonged fasting period preceding the dextrose tolerance test gives values from three to four times as high as are obtained with a starvation period of relatively short duration. Muscular activity before the test has no influence, but during the test may give a lower curve. Nausea during the test may result in a decrease in the alimentary hyperglycemia.

The amount of dextrose administered has no effect on the rise of the blood sugar. Large doses, amounting to 250 Gm and more, give a somewhat longer period of the high level, and usually the level does not return to normal as soon as with ordinary doses. Minimal doses, for example, 0.33 Gm per kilogram, give a small rise, but as little as 0.5 Gm per kilogram will give the usual curve. Repeated ingestions of dextrose result in a hyperglycemia only from the first dose. The hyperglycemia subsides even when dextrose is still present in the stomach. It has been found that 10 per cent dextrose is apt to leave the stomach more rapidly than a solution of higher or lower concentration. The blood sugar curve on different days for the same person may vary as much as 0.047 per cent, and the duration of the hyperglycemia curve may vary as much as forty-five minutes.

The second part of the report deals with observations on blood sugar in normal children as reported by others and with the results of the author's researches along these lines. According to other observers, the fasting blood sugar values range from 0.074 to 0.103 per cent. The tests were made at times that differ in relation to meals. Fasting periods under three hours are followed by many values above 0.100 per cent. Fasting periods longer than four hours result in values mostly under 0.100 per cent. On the whole, after four hours or more of fasting the blood sugar values have been found slightly lower in children than in adults, that is, from 0.080 to 0.085 per cent. In premature infants extremely low values have been reported, from 0.030 to 0.070 per cent. After protracted fasting periods of from one to several days the reports show a great variation. There has been no emotional influence demonstrated on blood sugar values in children.

The review of the blood sugar values after the ingestion of dextrose includes only those obtained from capillary and arterial blood, the results ranging from 0.029 to 0.057 per cent greater than in studies made on venous blood. Some authors reported that in children under 1 year of age the rise in blood sugar concentra-

tion in alimentary hyperglycemia follows within the same limits as in adults. Maximal values appear within from one-half to one hour, the duration of the alimentary hyperglycemia being less than three hours. The influence of protracted fasting on alimentary hyperglycemia in children has been found to be the same in two respects as in adults, namely, the carbohydrate tolerance is lower after protracted fasting, and a period of high protein and fat diet is followed by a lowered carbohydrate tolerance.

The author studied several groups of children. The first consisted of eleven new-born infants, from 4 to 14 days of age, on whom twenty-two examinations were done. The fasting period was from five to five and one-half hours, and the average fasting blood sugar value was 0.083 per cent, the values ranging from 0.066 to 0.099 per cent.

The second group was composed of twenty infants, from 15 days to 1 year of age, on whom forty-six examinations were made, the fasting period lasting from six to six and one-half hours. The average fasting value was found to be 0.080 per cent, with a range from 0.067 to 0.101 per cent. The third group was composed of six children, aged from 1 to 8 months, on whom twelve examinations were made. The fasting period lasted from six to six and one-half hours, and in this group saccharose was given in place of dextrose. The average fasting value was again found to be 0.080 per cent, with a range from 0.062 to 0.089 per cent. The fourth group consisted of twenty-two children, from 1 to 13 years of age, on whom forty-three examinations were made. The fasting period was from fourteen to fifteen hours. The average fasting value was 0.088 per cent, the values ranging from 0.068 to 0.099 per cent.

The author therefore concludes that in the first two weeks of life and in the first year of life there is a tendency to fasting blood sugar values which are lower than those in adults. In older children the values are the same as those usually observed in normal adults. The hyperglycemia is generally somewhat greater after the ingestion of dextrose, after saccharin, however, the reverse has been found. In six children, aged from 2 weeks to 3½ years, examinations were made after definite doses of dextrose, ranging from 1 to 10 Gm per kilogram of body weight. The so-called acceleration phenomenon was found to appear, but apparently at somewhat higher blood sugar values than in adults.

The author then reports observations made on blood sugar values in groups of children with celiac disease, cretinism, eczema, rickets and tetany. No observations were made on diabetic children. The clinical features of celiac disease, together with results of observations on blood sugar values as reported by other authors, were given. Svensgaard's investigations showed that none of the children whom she studied showed abnormalities of the fasting blood sugar values. The average fasting value was 0.085 per cent, with variations from 0.070 to 0.097 per cent.

The results of her study showed that in patients with celiac disease there is a tendency to an exceedingly slight hyperglycemia after the ingestion of dextrose. This peculiarity of blood sugar regulation appears remarkably constant in tests at intervals even of months and years, and even when these patients are examined during periods of definite improvement. A low blood sugar curve is therefore to be regarded as a sign of diagnostic importance in celiac disease. The author postulates that the slight alimentary hyperglycemia in celiac disease cannot be due primarily to an abnormality of the carbohydrate metabolism, but that it is a secondary result of an unusually rapid assimilation of the dextrose absorbed. The low blood sugar curve may then be due to an unusually rapid assimilation of the dextrose absorbed.

A review of the blood sugar values as found in myxedema and hyperthyroidism precedes the report of the author's investigation on blood sugar in cretins. She found that in cretinism the ingestion of dextrose gives only a rather low rise of the blood sugar curve, but that after treatment ingestion of the same dose of dextrose gives an extremely marked degree of hyperglycemia.

After reviewing the reported blood sugar studies in eczema, her own investigations are presented. In these children, after the ingestion of dextrose, she found a maximal value above 200 mg per hundred cubic centimeters somewhat more

frequently than in normal persons, but except for this rise, the blood sugar curve did not exceed the maximal values frequently found in normal children

In rickets and tetany, in contrast to reports of others, she found a normal alimentary hyperglycemia curve. She points out that all of the cases of tetany were complicated by rickets, which might conceal a possible difference in the blood sugar regulation. In tetany she found the fasting blood sugar values generally very low, less than 0.070 per cent, but after ingestion of dextrose there was a normal blood sugar curve, indicating that there was no radical change in the blood sugar regulation

**Classic Descriptions of Disease** By Ralph H. Major, M.D., Professor of Medicine, University of Kansas School of Medicine. Price, \$4.50. Pp 630, with 130 illustrations. Springfield, Ill. Charles C. Thomas, 1932

This book introduces one to the history of internal medicine in a most attractive manner. It republishes the original descriptions of many familiar clinical entities, methods of clinical diagnosis and methods of treatment. Practically the entire field of medicine and its development are covered from Hippocrates, with his description of the Hippocratic facies, to such recent work as the description of the early experiments with the use of insulin by Banting and Best, or the results of the administration of liver to the first group of patients with pernicious anemia so treated and reported by Minot. Each author mentioned has been selected carefully and represents a physician who has contributed observations of fundamental importance to the growth of knowledge in some particular field of internal medicine, and each quotation has been well chosen and is labeled with an accurate reference stating where the original is to be found. A short, lively, biographic sketch of each author accompanies his work, and often, also, a picture to give some idea of his appearance.

Dr. Major remarks in the preface to the book that the value of referring students to classic accounts of disease has been stressed by many of the greatest clinicians. His book is bound to be extremely useful to all teachers who believe in carrying on this method of instruction, and to all students with any historical bent. Naturally, by virtue of the material contained in it, the volume is filled with good writing. It makes a fine addition to any library.

**Proctoscopic Examination and the Treatment of Hemorrhoids and Anal Pruritus** By Louis A. Buie. Cloth. Price, \$3.50. Pp 178. Philadelphia. W. B. Saunders Company, 1931

The Mayo Clinic monograph on proctoscopic examination describes the methods of diagnosis and treatment of the rectal diseases at the Clinic. The first three chapters explain in detail their various instruments and methods of examining patients.

Under "Etiology of Hemorrhoids" the author considers the various factors and is of the opinion that infection plays the important role. Other proctologists believe that physical factors play a much more important part. The author considers sacral block as the anesthesia of choice because of better relaxation. From the reviewer's experience, complete relaxation can be obtained by circular infiltration with procaine hydrochloride. The chapter on "Hemorrhoidectomy" carefully describes the surgical procedures used by the author, and stresses the importance of postoperative care. Under "Treatment by Nonsurgical Methods" the technic is explained, along with the various solutions used and the complications following this method of treatment of hemorrhoids.

The various theories of pruritus ani are presented, along with the histopathologic changes. The author reports 84 per cent cures by the injection of 40 per cent ethyl alcohol subcutaneously, and stresses the importance of the care of the sloughing, which, he states, will accompany about half the injections. When used by inexperienced physicians, the dangers of such treatment are the extensive sloughing and stricture formation.

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